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EFNS/MDS-ES GUIDELINES/CME ARTICLE

EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease

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Background: A Task Force was convened by the EFNS/MDS-ES Scientist Panel on Parkinson's disease (PD) and other movement disorders to systemically review relevant publications on the diagnosis of PD.

Methods: Following the EFNS instruction for the preparation of neurological diagnostic guidelines, recommendation levels have been generated for diagnostic criteria and investigations.

Results: For the clinical diagnosis, we recommend the use of the Queen Square Brain Bank criteria (Level B). Genetic testing for specific mutations is recommended on an individual basis (Level B), taking into account specific features (i.e. family history and age of onset). We recommend olfactory testing to differentiate PD from other parkinsonian disorders including recessive forms (Level A). Screening for premotor PD with olfactory testing requires additional tests due to limited specificity. Drug challenge tests are not recommended for the diagnosis in de novo parkinsonian patients. There is an insufficient evidence to support their role in the differential diagnosis between PD and other parkinsonian syndromes. We recommend an assessment of cognition and a screening for REM sleep behaviour disorder, psychotic manifestations and severe depression in the initial evaluation of suspected PD cases (Level A). Transcranial sonography is recommended for the differentiation of PD from atypical and secondary parkinsonian disorders (Level A), for the early diagnosis of PD and in the detection of subjects at risk for PD (Level A), although the technique is so far not universally used and requires some expertise. Because

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specificity of TCS for the development of PD is limited, TCS should be used in conjunction with other screening tests. Conventional magnetic resonance imaging and diffusion-weighted imaging at 1.5 T are recommended as neuroimaging tools that can support a diagnosis of multiple system atrophy (MSA) or progressive supranuclear palsy versus PD on the basis of regional atrophy and signal change as well as diffusivity patterns (Level A). DaTscan SPECT is registered in Europe and the United States for the differential diagnosis between degenerative parkinsonisms and essential tremor (Level A). More specifically, DaTscan is indicated in the presence of significant diagnostic uncertainty such as parkinsonism associated with neuroleptic exposure and atypical tremor manifestations such as isolated unilateral postural tremor. Studies of [^{123}I]MIBG/SPECT cardiac uptake may be used to identify patients with PD versus controls and MSA patients (Level A). All other SPECT imaging studies do not fulfil registration standards and cannot be recommended for routine clinical use. At the moment, no conclusion can be drawn as to diagnostic efficacy of autonomic function tests, neurophysiological tests and positron emission tomography imaging in PD.

Conclusions: The diagnosis of PD is still largely based on the correct identification of its clinical features. Selected investigations (genetic, olfactory, and neuroimaging studies) have an ancillary role in confirming the diagnosis, and some of them could be possibly used in the near future to identify subjects in a pre-symptomatic phase of the disease.

Introduction

A correct diagnosis of Parkinson's disease (PD) is a prerequisite for patient counselling and therapeutic management. Despite all the recent advances in imaging and genetics of parkinsonian disorders, the diagnosis of PD remains a primarily clinical exercise. However, clinical diagnostic uncertainty is high at initial presentation, and up to 10–30% of patients initially diagnosed as PD are clinically re-classified even in specialized units [1]. Targeting this pitfall, numerous ancillary investigations have been developed in the last decades to support PD diagnostic work-up [2]. Because these tests differ in their differential diagnostic performance, availability and costs, the EFNS/MDS-ES Task Force identified a clear need to develop guidelines for the diagnosis of PD to be applied across Europe. This need is fostered by recent efforts of the PD research community focusing on the development of screening tools capable of identifying individuals *at risk* for PD.

This EFNS/MDS-ES Task Force report is divided into nine sections addressing key aspects of the diagnostic work-up of patients presenting with parkinsonism:

1 Clinical diagnostic criteria
2 Genetic testing
3 Autonomic function testing
4 Olfactory tests
5 Drug challenge tests
6 Neurophysiological tests
7 Neuropsychological tests
8 Neuroimaging
9 Economic issues

Groups of experts were allocated to each section and asked to provide an evidence-based recommendation level for the assigned diagnostic tool. To this end, MEDLINE, EMBASE and Cochrane libraries were searched for relevant citations up to June 2011. Consensus on the guidelines was finally reached within the Task Force.

The recommendations have been developed according to the EFNS Evidence Classification Scheme for diagnostic measures [3].

In this statement, recommendations for diagnostic investigations in PD are therefore graded as follows:

- Level A – effective
- Level B – probably effective
- Level C – possibly effective

A Level A or B recommendation does not mean that this test should be employed in all patients of a certain group, but simply means that the test has good diagnostic accuracy. It is for the physician to decide whether or not to use it in the given patient. For example, a Level A recommendation for an imaging test based on excellent diagnostic performance may still not mean that a clear-cut patient with a solid clinical diagnosis should have this test.

Section 1: clinical diagnostic criteria for PD

Several sets of clinical diagnostic criteria have been proposed, based mainly on the presence of the classi-

Table 1 Queen Square Brain Bank UK PDS Brain Bank Criteria for the diagnosis of PD [4,6]

Step 1 Diagnosis of parkinsonian syndrome
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions) and at least one of the following:

- Muscular rigidity
- 4- to 6-Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative (*)
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language and praxis
- Babinski sign
- Presence of a cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of L-dopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria of Parkinson's disease
Three or more required for the diagnosis of definite Parkinson's disease:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side onset most (*)
- Excellent response (70–100%) to L-dopa
- Severe L-dopa-induced chorea
- L-dopa response for 5 years or more (*)
- Clinical course of 10 years or more (*)
- Hyposmia
- Visual hallucinations

(*) Criteria that will need future revision.

cal motor signs of the disease, combined with the absence of incompatible or atypical signs (the so-called red flags suggestive of atypical parkinsonism). The most widely used clinical criteria for the diagnosis of PD are those introduced by the Queen Square Brain Bank (QSBB) [4]. These criteria provide a three-step method: (Table 1)

1 Signs that *must* be present
2 Signs that should *not* be present
3 Supportive criteria

The first diagnostic step requires the presence of bradykinesia. Crucially, bradykinesia is not just slowness of movement or movements. It is rather meant as *progressive fatiguing and decrement of repetitive alternating movements* during finger or foot tapping [5]. The second step involves a checklist of symptoms and signs that argue against a diagnosis of PD. Finally, the diagnosis of PD requires the presence of three or more supportive criteria (Table 1). Recently, hyposmia and hallucinations have been added to this list [6].

The accuracy of the QSBB clinical diagnostic criteria has been retrospectively assessed in two clinical–pathological studies (class III evidence) [7], (class III evidence) [8]. In a series of 100 cases with pathologically proven PD, the QSBB clinical diagnostic criteria were applied retrospectively, and the diagnostic accuracy proved to be 82% [7]. A more recent study (published 10 years after the previous publication) involved a series of 143 cases with pathologically proven PD. In this study, the QSBB clinical diagnostic criteria were mostly applied by movement disorder experts [8]. The results showed an overall sensitivity for PD clinical diagnosis of 91.1%, a specificity of 98.4%, a positive predictive value of 98.6% and a negative predictive value of 90%. The clinical diagnostic accuracy was thus improved over time, suggesting an optimized use of the QSBB criteria and its supportive and non-supportive signs.

Clinical expertise of the neurologist assessing PD diagnosis has been shown to predict the diagnostic effectiveness of the QSBB clinical diagnostic criteria in two independent studies [1,9]. In the first study, the QSBB clinical diagnostic criteria were applied by movement disorder specialists to 402 cases previously diagnosed as PD from general practitioners in North Wales [9]. A definite diagnosis of PD could be reached in only 53% of cases, suggesting an error rate of 47% outside of specialized centres. The most common misdiagnoses were essential tremor, Alzheimer's disease and vascular parkinsonism. The second study compared the diagnostic accuracy of PD clinical diagnosis, as made by movement disorder experts, in comparison with non-expert physicians in the community [1]. In this study, 126 patients with a pre-existing clinical diagnosis of probable or possible PD underwent diagnostic reassessment by movement disorder specialists using the QSBB clinical diagnostic criteria. The results showed that experts reached a greater sensitivity (93.5% for experts versus 73.5% for non-experts) and positive predictive value (88.7% for experts versus 73.5% for non-experts), whereas the negative predictive value was similar (76.9% for experts versus 79.1% for non-experts) [1]. These

results underscored a relatively high diagnostic inaccuracy by non-experts.

Even if made by a movement disorder expert, PD diagnosis may change at follow-up, for several reasons: development of atypical signs (red flags), insufficient response to dopaminergic treatment or neuroimaging clues for an alternative diagnosis.

In prospective studies with PD cohorts initially recruited from experts according to the QSBB criteria, change of diagnosis occurred in 6–8% of cases [10,11]. This suggests a relative low rate of misclassification, if the diagnosis is initially assessed by a movement disorder expert.

Although the QSBB clinical diagnostic criteria are widely used in clinical practice, a number of pitfalls have been recognized:

1 Having more than one affected relative cannot be considered an exclusion criterion of PD anymore;
2 Some of the supportive criteria such as persistent asymmetry, prolonged disease course or continuous levodopa response may occur in atypical parkinsonian disorders as well. A critical revision of the QSBB criteria will be required to address these drawbacks.

Other diagnostic criteria are shown as supporting information in the online version of this article (Data S1).

Recommendations

Only the QSBB clinical diagnostic criteria have been validated by Hughes *et al*. [8] and are therefore recommended as *probably effective* (Level B) for clinical practice.

Section 2: genetic testing

These recommendations are formulated according to the criteria established by the EFNS [3], with some modifications accounting for the specific nature of genetic tests [12]. Genetic testing is by definition the gold standard for the diagnosis of a genetic disease (barring the rare event of a laboratory error). Therefore, the diagnostic accuracy of genetic testing cannot be measured by using another method as reference investigation. Therefore, the level of recommendation for genetic testing has been based on the quality of available studies investigating the nature and frequency of mutations of a given gene amongst clinically defined series of patients.

Because all the available studies have been retrospective (i.e. looking for specific mutations amongst previously ascertained and clinically diagnosed series) and because the formal execution of the genetic testing on anonymously coded DNA samples by laboratory technicians can be practically considered as equivalent to a blinded testing condition, the studies are classified as class III evidence, which leads to Level B recommendation.

With few notable exceptions in some populations, <5% of all PD cases are caused by known single-gene mutations. Therefore, genetic testing will allow an accurate aetiological diagnosis only in a minority of patients [12,13]. As no specific treatment is available for genetic cases, the purpose of genetic testing in PD is essentially oriented at patient and family members' counselling with respect to disease prognosis and genetic risk of unaffected relatives.

The results of diagnostic genetic testing have implications in the psychological, social and professional domains of both patients and relatives. Therefore, informed consent and privacy warranty are important issues. Further, the genetic testing should always be performed by a professional team and include pre-test and post-test counselling [12].

Autosomal dominant forms of PD

SNCA

Point mutations in the gene for alpha-synuclein (SNCA), as well as duplications and triplications of the entire gene locus, can cause PD. The point mutations E46K and A53T and also gene triplications cause an aggressive form of PD with relatively early onset [14]. Most cases have been identified in families with multiple affected individuals. The A30P mutation, as well as SNCA duplications, causes more typical PD with late onset. Incomplete penetrance of SNCA duplications may result in a negative family history [15]. Nevertheless, all the above cited SNCA mutations are rare in sporadic patients.

Leucine-rich repeat kinase 2

Mutations in the gene for leucine-rich repeat kinase 2 (LRRK2) are a much more common cause of dominant PD. Up to date, 6 mutations are known to be pathogenic (N1437H, R1441C, R1441G, Y1699C, G2019S and I2020T), based on their cosegregation in PD families. Overall, LRRK2 mutations account for 5–15% of dominant familial [16], and 1–3% of sporadic PD cases [17], with higher prevalence of some founder mutations in specific populations. The G2019S variant is found in 15–30% of Ashkenazi Jewish [18] and up to 40% of North African Arab patients (both sporadic and familial), whilst the R1441G variant is a Basque founder mutation with a prevalence of 15% in patients with PD from this region [19].

Clinically, LRRK2-associated PD is indistinguishable from sporadic typical PD, as to age of onset and symptomatology. Reduced penetrance of 30–70% has been estimated for the G2019S mutation.

Glucocerebrosidase

Heterozygous mutations in the gene for glucocerebrosidase (GBA) are a frequent and strong risk factor for PD, especially in some populations [20–22]. Some mutations are more prevalent in specific ethnic groups, such as the N370S mutation amongst Ashkenazi Jewish. According to current odds ratios' estimates (pooled OR > 5), *GBA* mutations have much lower effect size than classical mendelian mutations. In other words, GBA mutations display a markedly reduced penetrance. However, an accurate estimate of ORs and penetrance is currently possible only for the most common *GBA* mutations. Clinically, patients with *GBA* pathogenic mutations have typical PD with possibly slightly earlier-onset age.

Autosomal recessive forms of PD

Homozygous or compound heterozygous mutations in each of the following three genes: *parkin* (PARK2), *PINK1* (PARK6) and *DJ-1* (PARK7), can cause autosomal recessive forms of PD. Mutations in the *parkin* gene are the most common. Up to half of familial PD cases with a disease onset under the age of 45 and a recessive pattern of inheritance are caused by *parkin* mutations. Similarly, *parkin* mutations underlie ~15% of the sporadic PD cases with disease onset before the age of 45 [23]. Mutations in the *PINK1* and *DJ-1* gene are less common, accounting for up to 1–8% and 1–2% of the sporadic cases with early onset, respectively. The likelihood of PINK-1 and DJ-1 mutations is inversely proportional to the age of PD onset: the earlier the onset, the higher the likelihood. A large number of mutations have been identified in these three genes worldwide, including point or small mutations, but also large genomic rearrangements (deletions and multiplications). The latter are especially frequent in the *parkin* gene. Therefore, sequencing and dosage assay of all exons is required for an accurate screening of these three genes.

In some cases, only a single heterozygous mutation is detected in one of the genes for recessive PD. This finding does not lend itself to a clear interpretation. On the one hand, a single heterozygous mutation might be coincidental (unrelated to the disease), as supported from the screening of large case–control series [24]. On the other hand, a single heterozygous mutation in one of these genes might also act as a risk factor for PD. Last, a second pathogenic mutation might be present, but escapes detection by the standard screening methods.

The clinical phenotype associated with *parkin* mutations is characterized by early-onset parkinsonism, good and prolonged L-dopa responsiveness and overall benign course. The average age at onset is in the 30s in most patients, but late-onset cases have been described as well. Motor fluctuations and levodopa-induced dyskinesias are frequent, whereas marked cognitive or autonomic disturbances are rare [25]. The phenotype associated with *PINK1* and *DJ-1* mutations has been studied in a smaller number of patients, but it is basically indistinguishable from that of *parkin*.

Atypical recessive forms

Mutations in the *ATP13A2* (*PARK9*), PLA2G6 (*PARK14*), FBXO7 (*PARK15*) and other genes cause rare recessive forms of parkinsonism, usually with very early onset (<30 years) and atypical features (pyramidal, dystonic, ocular movement and cognitive disturbances).

Recommendations

Available evidence provides a Level B recommendation for the use of genetic testing in the diagnosis of PD. Genetic testing for specific mutations is recommended on an individual basis, and specific features, particularly family history and age of onset, must be taken into account:

I Testing for *SNCA* point mutations and gene multiplications is recommended only in families with multiple affected members in more than one generation suggestive of dominant inheritance, with early- or late-onset PD

II *LRRK2* genetic testing for counselling purposes, specifically directed at known pathogenic variants is recommended in patients with a clinical picture of typical PD and a positive family history suggestive of dominant inheritance

III In sporadic patients, genetic testing should be limited to the search for known *LRRK2* founder mutations in the appropriate populations (i.e. with known high mutation frequencies)

IV Genetic testing for GBA gene mutations is recommended in patients with typical PD with or without a positive family history, limited to the known founder mutations of established pathogenic role in the appropriate populations

V Genetic testing of the *parkin*, *PINK1* and *DJ-1* genes for counselling purposes is recommended in

patients with typical PD and positive family history compatible with recessive inheritance, particularly when the disease onset is before the age of 50 years. For sporadic cases, *parkin*, *PINK1* and *DJ-1* genetic testing is recommended when onset is very early, particularly before the age of 40

VI Testing of the *ATP13A2, PLA2G6* and *FBXO7* genes might be considered in cases with very-early-onset PD, if no mutation in *parkin*, *PINK1* and *DJ-1* gene has been found.

Section 3: autonomic function tests

Symptoms suggestive of autonomic failure are common in PD, with increasing prevalence and severity as the disease progresses. A subgroup of patients with PD develop autonomic symptoms such as orthostatic hypotension (OH), urogenital failure or constipation early on, sometimes even prior to motor onset. Differentiation from multiple system atrophy (MSA) on clinical grounds may be difficult in this situation. Recognition of autonomic failure in PD by means of appropriate autonomic function tests (AFTs) is important because of diagnostic and therapeutic implications. Most reports on AFTs in PD represent class IV evidence. AFTs comparing PD and MSA patients have reported the differences between the two diseases in cardiovascular [26–28], urinary [29–31], anorectal [32], skin temperature and sweating regulatory functions [27,28,33,34]. However, multiple studies have shown that cardiovascular AFTs alone do not distinguish between PD, MSA and progressive supranuclear palsy (PSP) [35,36]. Detrusor-sphincter dyssynergia, large post-void residuals and an open bladder neck are common urodynamic findings in MSA [30], whilst these are usually less pronounced in idiopathic PD [37]. Anorectal manometric patterns do not differentiate MSA from PD patients. Both MSA and PD patients may show an abnormal straining pattern, decreased anal tone or both dysfunctions. However, in MSA, sphincter abnormalities occur earlier and develop faster than in PD [32].

Thermoregulatory sweat tests have been investigated in PD and MSA with controversial results [35,38]. In one study [35], MSA and PD patients showed similar patterns of anhidrosis. In a second study, progressively wider anhidrotic skin areas could be shown in MSA [38]. Skin temperature and blood flow measurements have been proposed to discriminate MSA from PD (cold hand sign). However, there is considerable overlap between these disorders [33,39].

In general, most of the AFT studies segregated patients with parkinsonism according to clinical diagnostic criteria into MSA or PD depending on the presence of overt autonomic failure. This may have increased the likelihood of abnormal test results in MSA patients. Unbiased AFT data are sparse, suggesting substantial overlap between MSA and PD patients (class III evidence) [35].

Neurophysiological assessment of autonomic function

In contrast to PD and other degenerative parkinsonian syndromes, R-R interval variation at ECG examination is reduced and the sympathetic skin response is abnormal in MSA [27]. These tests might be used for the differentiation of MSA from other parkinsonian syndromes.

Recommendations

Autonomic function tests are principally helpful to detect autonomic impairments in patients with PD. Some dysautonomic features, like OH or post-void residual volume, have important therapeutic implications. However, at the moment, there is insufficient evidence to provide a level of recommendation for AFTs in PD.

Section 4: olfactory tests

The reported prevalence of olfactory deficit in PD ranges from 73% to 90% [40–45]. The best validated and most widely used quantitative screening tests for odour identification are the UPSIT and the smell test. The smell test is also available with ethnically specific odours [class I, 40–45]. In contrast to PD, published data suggest that olfactory function is mildly impaired or normal in MSA, essential tremor, PSP and corticobasal degeneration (CBD) [class I, 45–47]. Also, short reports indicate that in vascular parkinsonism and drug-induced parkinsonism, olfactory function is mostly unaffected [class I, 48,49]. In monogenic PD, especially in the recessive forms, olfactory dysfunction is less impaired than in PD [class I, 50,51]. Current evidence suggests that odour detection and identification deficits are rather independent of the disease stage, duration or the use of antiparkinsonian medication. To the contrary, impairment of odour discrimination increases with disease progression, although controversial results have been obtained in different studies [class I, 40,41,43]. Impaired olfaction is nowadays recognized as non-motor symptom of PD that may be detectable even in the pre-motor stage [class I, 52–55]. Smell identification score appears to correlate with sympathetic denervation of the heart measured with iodine-123-labelled meta-iodobenzylguanidine

(MIBG) in early PD patients [56]. Several independent studies have shown that hyposmia positively predicts the development of PD [class I, 52,55,57–59]. According to population-based (class I evidence) [52] and other prospective studies (class I evidence) [53–55], sensitivity of hyposmia for the identification of individuals at risk for PD is high (>80%), but specificity is low as up to one-third of the elderly population has olfactory loss.

Recommendations

Olfactory testing differentiates PD from
I Atypical and secondary parkinsonian disorders (Level A).
II Recessive forms of PD (Level A).

Current evidence suggests that olfactory testing may be considered as a diagnostic screening procedure (Level A), but not as an indicator of disease progression (Level B) in PD. Olfactory testing is a sensitive screening test for pre-motor PD (Level A), but not specific. Thus, olfactory testing can be envisioned in a screening battery for PD. If hyposmia is detected, then other specific tests for PD should follow.

Section 5: drug challenge tests

The clinical diagnosis of PD is supported by a favourable response to dopaminergic drugs, whilst a failure represents an exclusion criterion. Based on this assumption, acute challenge tests with various compounds have been proposed since the 1980s as predictors of long-term L-dopa responsiveness and as supportive criterion for PD diagnosis [60–64].

Heterogeneous methodologies (e.g. levodopa versus apomorphine, high dose versus low dose, fixed dose versus flexible dose based on the body weight) have influenced the results of the above-mentioned studies to a great extent. They have also impacted on the practical use of the test (part of the initial screening in de novo patients or re-evaluation in patients with a previous diagnosis of PD or other parkinsonian conditions). Additionally, no agreement exists on the definition of a positive response to a drug challenge.

A comprehensive systematic review of studies examining the diagnostic accuracy of acute challenge tests with levodopa and/or apomorphine in the diagnosis of PD versus other parkinsonian syndromes was published in 2000 [65]. The authors of this review concluded that the accuracy of the acute challenge tests is similar to that of chronic levodopa therapy, essentially providing no further clues for the differential diagnosis of parkinsonian syndromes. As most patients will eventually be scheduled for dopaminergic medications, these tests provide limited positive diagnostic benefit at the expense of adverse events.

Almost contemporarily, a consensus meeting on the role of acute dopaminergic challenge in PD was held [66]. Conclusions from this meeting were summarized in a subsequent paper, which described the scientific background and supplied practical guidelines to perform and evaluate acute challenge tests in parkinsonian disorders. In particular, the consensus meeting participants agreed that lack of motor improvement following an acute challenge in a drug-naive parkinsonian patient, or in a patient at treatment beginning, does not always exclude a positive chronic response. The false-negative rate of dopaminergic challenge tests in drug-naive patients, as to prediction of L-dopa chronic responsiveness, may be as high as 40%. Furthermore, following a negative response to apomorphine, an additional levodopa challenge may be warranted, because it has been occasionally reported that patients who do not respond to apomorphine may respond to levodopa.

In a more recent statement from a Committee of the American Academy of Neurology (AAN) [67], it was recognized that levodopa and apomorphine challenge tests are probably useful in distinguishing PD from other parkinsonian syndromes. This conclusion was drawn because of two studies (class I evidence) [68] (class III evidence) [69]. The members of the AAN Committee concluded that diagnostic yields appear to be similar between the two tests. In addition, the committee highlighted a relative high rate of false-negative and false-positive results. Further, according to AAN Committee, these studies generated insufficient evidence due to the lack of post-mortem validation.

Recommendations

Drug challenge tests are not recommended for the diagnosis of de novo parkinsonian patients. There is an insufficient evidence to support their role in the differential diagnosis between PD and other parkinsonian syndromes.

Section 6: neurophysiological tests

EEG

Routine EEG can be useful in PD patients with suspected dementia, but it cannot differentiate PD from other parkinsonian disorders [70,71].

Evoked potentials

A number of unblinded multimodal evoked potential studies have been performed in PD versus demented or atypical parkinsonian patients, showing some differences that may help in the differential diagnosis of parkinsonian syndromes, if confirmed in prospective blinded studies [72–96].

Sleep studies

Polysomnography can be used to investigate REM and other sleep disorders, as well as excessive daytime sleepiness. The latter are frequent in PD and MSA, but uncommon in other types of degenerative parkinsonism [97–101].

Tremor analysis

Tremor analysis can help differentiate parkinsonian rest and postural tremor from other causes of tremor [102–105].

EMG/ENG studies

Routine EMG/ENG studies are usually normal in PD. Anal sphincter EMG is usually normal in PD, whereas it can be abnormal in atypical parkinsonism, particularly in MSA [106–108].

Recommendations

No recommendation can be given on neurophysiological tests because of the low evidence level of the available studies.

Section 7: neuropsychological tests

The assessment of cognitive and neuropsychiatric function in the diagnostic work-up of PD is more aimed at the exclusion of *other* parkinsonian disorders, than being confirmatory for the diagnosis of PD. For example, the combination of parkinsonism and dementia at first presentation could be suggestive of dementia with Lewy bodies (DLB), or even Alzheimer's disease, whilst prominent frontosubcortical cognitive impairment could point more towards a diagnosis of PSP [109,110].

This is not to say that cognitive impairment at baseline is incompatible with the diagnosis of PD. A recent multicentric pooled analysis of 1346 patients with PD from eight different cohorts found that 25.8% (95% CI: 23.5–28.2) had mild cognitive impairment [111]. Several of these cohorts had examined incident cases. By definition, this cognitive impairment is insufficient to interfere with activities of daily living, and the patients are thus not demented.

Collateral history from a carer is helpful in determining the effects (if any) of cognitive impairment upon daily function. The National Institute of Neurological Disorders and Stroke (NINDS) PD Common Data Elements (CDEs) has recently recommended scales that can be readily used in data collection for clinical trials that are as broad as possible and applicable to all stages of PD. In terms of screening for PD dementia (PDD), the Mattis Dementia Rating Scale (DRS-2), a validated instrument for the diagnosis of PDD [112], scored most highly, but is impractical in routine clinical practice because of the time it takes to administer [113]. Other scales that were recommended for screening purposes were the Addenbrooke's Cognitive Examination-Revised (ACE-R) [114,115] and the Montreal Cognitive Assessment (MoCA) [116,117]. Both the ACE-R and the MoCA are freely available. Two scales specifically developed to rate cognitive functions in PD, the SCOPA-cog [class I, 118] and the PD-CRS [class I, 119], are also suitable for research purposes and interventional trials [120]. The PD-CRS has the additional advantage of distinguishing frontosubcortical and posterior cortical patterns of cognitive impairment [121]. It was considered by the NINDS review as being comprehensive, sensitive (94%) and specific (94%) in screening for PDD, and able to distinguish between PD, mildly cognitively impaired and demented PD patients. Although widely used, the Mini Mental State Examination (MMSE) does not capture domains germane to PD (i.e. executive dysfunction) and suffers from ceiling effects (i.e. a normal score does not rule out cognitive disturbances or dementia in PD). The sensitivity of this instrument in the context of detecting dementia in PD may be improved considerably by the addition of simple tests (i.e. immediate and delayed recall, verbal fluency and a 'pill questionnaire') [122]. Nevertheless, other brief screening instruments may help in clinical practice to accurately and quickly screen for PDD. The recently developed PDD short screen (PDD-SS) (class I evidence) [123] is a brief screening test displaying similar accuracy as the DRS-2 for the diagnosis of dementia with a considerable shorter administration time (5–7 min).

Regarding neuropsychiatric function, we recommend the brief assessment of sleep, mood and psychosis, as these features may have diagnostic significance for PD. A history suggestive of REM sleep behaviour disorder (RBD) would be suggestive of a 'synucleinopathy', but the presence of RBD would not itself differentiate between PD, DLB and MSA. On the other

hand, the presence of RBD in a patient with an undiagnosed tremor disorder would point against essential tremor or dystonic tremor. Significant depressive disorder can confound cognitive assessment and should be screened for, whilst spontaneous visual hallucinations (i.e. occurring in the absence of dopaminergic treatment) could be suggestive of DLB.

Again, collateral history from a carer is useful to determine behavioural change, sleep disorders and psychotic features. Polysomnography is the 'gold standard' for the diagnosis of RBD, but impractical in routine clinical assessment. The RBD Screening Questionnaire has a sensitivity of 0.96 and a specificity of 0.56 for the diagnosis of RBD when a cut-off of five points is applied (class I evidence) [124]. Part I (Non-Motor Aspects of Experiences of Daily Living) of the MDS-UPDRS includes validated screening questions for hallucinations and psychosis, as well as depressed mood, and is recommended as a 'clinician-friendly' screening instrument (class I evidence) [125].

Recommendations

An assessment of neuropsychological functioning in a person presenting with parkinsonism suspected of being PD is recommended (Level A) and should include

I A collateral history from a reliable carer

II A brief assessment of cognition

III Screening for RBD, psychotic manifestations and severe depression.

Section 8: neuroimaging

Transcranial sonography

Because hyperechogenicity of the substantia nigra (SN) was first described by means of transcranial sonography (TCS) in PD more than 15 years ago, the finding has been confirmed by many groups all over the world [126–134] (although the utility is not universally accepted and TCS is infrequently performed in several countries including the USA). Guidelines for the assessment of nigral hyperechogenicity have been published [135–137], and the technique is being used at an increasing number of places for diagnostic and scientific purposes concerning parkinsonian syndromes.

Applying high-end ultrasound systems with standardized settings [135–138], the resolution of intracranial structures is, with 0.7×1.1 mm in the focal zone, very high [139]. Similarly, a satisfactory reproducibility is indicated by an intra- (ICC 0.96 and 0.93, respectively, for both hemispheres) and inter-rater reliability (ICC 0.84 and 0.89) for quantitative computerized SN planimetry [140].

For the diagnostic work-up of parkinsonian syndromes, two standardized scanning planes are used:

- The mesencephalic scanning plane in which the SN, the red nucleus and the hyperechogenic midline (brainstem raphe) are visible (Fig. 1);
- The third ventricular plane in which the ventricular system and the normally hypoechogenic basal ganglia can be delineated.

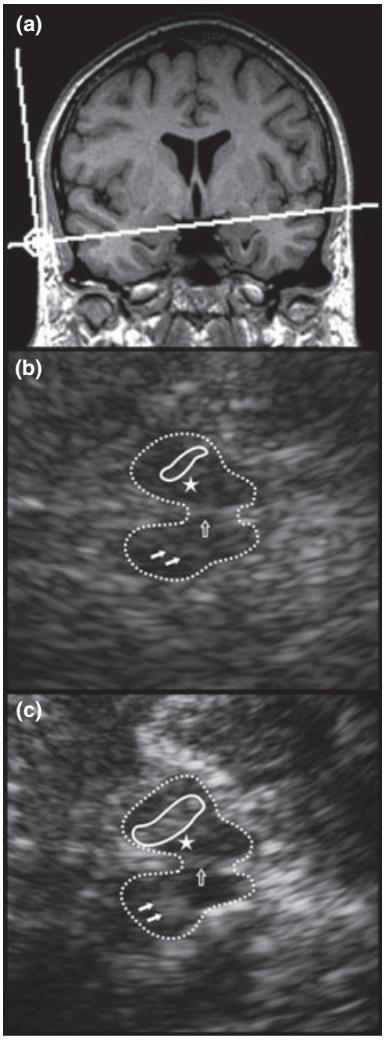

Figure 1 Transcranial sonography of the mesencephalic brainstem. The mesencephalic brainstem is scanned parallel to the orbito-meatal line (a). (b) Depicts the mesencephalic brainstem (surrounded by dotted line) of a healthy control with normal echogenicity of the substantia nigra (SN) (encircled ipsilaterally and marked with arrows contralaterally to the insonating probe), the area of the red nucleus (asterisk) and the hyperechogenic midline raphe (open arrow). In a patient with Parkinson's disease (PD), the area of hyperechogenicity at the anatomical site of the SN is enlarged (c; encircled ipsilaterally and marked with arrows contralaterally).

Planimetric measurement of the area of hyperechogenicity at the anatomical site of the SN enables the categorization of SN echogenicity into normal or abnormal according to cut-off values established with reference to percentile ranks assessed in healthy cohorts.

Substantia nigra areas are classified as *markedly hyperechogenic* (above the 90th percentile of the healthy population) or *moderately hyperechogenic* (between the 75th and 90th percentile, see also [135–137]). Measurement of the ventricular system and semiquantitative assessment of the basal ganglia are primarily important for the differential diagnosis of PD.

For clinical practice, it is important to realize that proper evaluation of the SN depends on

- Application of ultrasound-specific cut-offs
- Quality of the temporal bone window – in about 10% of the Caucasian population, the transtemporal bone window is not sufficient to depict the relevant structures
- To some extent experience of the investigator (see also [141]).

The current evidence suggests that TCS is useful in the diagnosis of parkinsonian syndromes, especially with regard to

- Differentiation of atypical parkinsonian syndromes (APS; class I evidence, Level A) [142]
- Differentiation of secondary parkinsonian syndromes (class I and II evidence, Level A – for sensitivity, specificity and predictive value of parameters) [132]
- Early diagnosis of PD, in clinically unclear cases (class II evidence) [143]
- Detection of subjects at risk for PD (class I) including asymptomatic mutation carriers for monogenic forms of PD [133–150].

Substantia nigra hyperechogenicity occurs in about 10% of the healthy population [151,152], a proportion much larger than the prevalence of PD, and may occur in a much smaller proportion in subjects with other neurodegenerative disorders [133,153–156], frequently in heavy metal storing diseases [157–159] and sometimes in neuroinflammatory disorders [160]. Because specificity for the development of incident PD is about 80%, the application of TCS should be therefore combined with other screening procedures.

Stability of SN hyperechogenicity during the disease course is still an unclear issue. Most reports argue for a stable area of echogenicity [126,136,161,162], which, however, may increase with age [163], thus hindering its use as progression marker in PD.

Recommendations

Transcranial sonography is recommended (Level A) for

I Differential diagnosis of PD from APS and secondary parkinsonian syndromes

II Early diagnosis of PD

III Detection of subjects at risk for PD

The technique is so far not universally used and requires some expertise. Because specificity of TCS for the development of PD is limited, TCS should be used in conjunction with other screening tests.

Magnetic resonance imaging

In clinical practice, conventional magnetic resonance imaging (cMRI) with visual assessment of T2- (sensitive to changes in tissue properties, including tissue damage) and T1-weighted (important for anatomical details providing good grey matter/white matter contrast) imaging is a well-established method for the exclusion of symptomatic [164] (class IV evidence studies available – for review, see [164]).

Several findings on conventional structural MRI have been described as diagnostic markers of MSA (See Table 2). These include atrophy and signal alterations at 1.5 T in the putamen and several infratentorial regions, such as

- Hyperintense putaminal rim with or without hypointensity in the dorsolateral part of the putamen (Fig. 2)
- 'Hot cross bun' sign of the pons (Fig. 3)
- Atrophy of the cerebellum
- Hyperintensity in the middle cerebellar peduncle (MCP)

compared to PD, PSP and controls as well as pontine and putaminal atrophy compared to PD and controls (class II evidence) [165–168]; (class III evidence) [167–169,169–175]; (class IV evidence) [176]. Specificity of the aforementioned abnormalities in differentiating MSA from PD and healthy controls is considered quite high, whereas sensitivity – particularly in early disease stages – seems to be insufficient [164]. However, sensitivity of signal alterations can be somewhat improved by modifying technical aspects such as spatial resolution by using thinner slices or modifying relaxation contrast by using T2*-weighted gradient echo sequences [168,174].

Other abnormalities in MSA-P, which may provide a differentiation from PD, PSP and controls, include

- Posterolateral linearization of the putaminal margin (versus convex in controls) (class III evidence) [177]
- Putaminal hyperintensity on T1-weighted images (class III evidence) [169]

Table 2 Routine MRI findings in atypical parkinsonism [2,164]

Multiple system atrophy

- Putaminal atrophy
- Putaminal slit sign
- Putaminal hypointensity
- Pontine and/or bulbar atrophy
- Cerebellar and/or dentate atrophy
- Atrophy of the MCP
- Reduced MCP diameter (< 8.0 mm in reference [188])
- Dilatation of the fourth ventricle
- Signal increase in MCP
- Signal increase in cerebellum
- Signal increase in inferior olives
- Signal increase in pontine fibres (hot cross bun sign)

Progressive supranuclear palsy[a]

- Midbrain atrophy
- Indirect signs of midbrain atrophy:
  - Reduced AP midbrain diameter (< 14 mm in reference [190])
  - Abnormal superior midbrain profile[b]
  - '(king) penguin silhouette' or 'hummingbird' sign[c]
  - Reduced ratio between midbrain and pontine areas
  - Increased MRPI[d]
- Dilatation of the third ventricle
- Atrophy of the SCP
- Signal increase in SCP (on FLAIR images)
- Signal increase in globus pallidus
- Signal increase in red nucleus
- Putaminal atrophy
- Frontal and parietal atrophy

Corticobasal degeneration[e]

- Cortical atrophy (mostly frontoparietal and asymmetric, sometimes even global and symmetric)
- Putaminal hypointensity[f]
- Hyperintense signal changes in the motor cortex or subcortical white matter

Signal changes refer to 1.5-Tesla MRI scanners.
MCP, middle cerebellar peduncle; SCP, superior cerebellar peduncle; AP anterior–posterior; MRPI, MR parkinsonism index.
[a]Almost all MRI studies of PSP included patients suffering from the most reliably identifiable classic picture of PSP (i.e. Richardson's syndrome).
[b]Flat or concave versus convex aspect in healthy people.
[c]The shapes of the midbrain tegmentum (the bird's head) and pons (the bird's body) resemble a lateral view of a standing king penguin or hummingbird.
[d]MRPI: multiplying the ratio of pontine to midbrain area by the ratio of the MCP to SCP width.
[e]Given the pathological heterogeneity of a 'corticobasal syndrome', including CBD and other neurodegenerative causes such as PSP, Pick's disease and other frontotemporal lobar degenerations, MRI studies of clinically defined CBD must be discussed with a grain of caution.

Further, visual assessment of

- Atrophy of the superior cerebellar peduncle (SCP) (class II evidence) [178]
- 'Penguin silhouette' or 'hummingbird' sign (where the shapes of the midbrain tegmentum – that is, the bird's head – and pons – that is, the bird's body – resemble a lateral view of a standing king penguin or hummingbird; Fig. 4) on midsagittal MR images (class II evidence) [179]; (class III evidence) [180]; (class IV evidence) [181]
- Enlarged 3rd ventricle (class II evidence) [182]; (class III evidence) [171,173]

can point the diagnosis towards PSP versus PD, controls and MSA (Level C), whereas visual assessment of midbrain atrophy may point out a diagnosis of PSP versus PD or controls (class III evidence) [171,173,175].

Putaminal, pontine and midbrain atrophy seems to occur in both MSA and PSP patients, although putaminal and pontine atrophy is more common in MSA and midbrain atrophy more common in PSP [171,173]. Other abnormalities in PSP include an abnormal superior profile of the midbrain (flat or concave versus convex aspect in healthy people) compared to patients with PD and controls [183] (class III evidence) [183] and increased signal changes in the SCP on FLAIR images compared to controls, PD and MSA patients [184] (class III evidence) [183].

Simple quantitative measures of diameters, areas and volumes including region of interest (ROI)-based assessment of various structures on MRI have been applied as an indirect measure of brain structures known to be atrophic in different parkinsonian disorders for the differential diagnosis of neurodegenerative parkinsonism. Volume loss of different supratentorial and infratentorial brain structures, measured by MR volumetry (MRV) with semi-automatic segmentation techniques on a ROI approach, has been reported in patients with APS, whereas most studies were not able to detect such volume differences between patients with PD and controls, whilst with advancing disease hippocampal atrophy has been reported in patients with PD compared to healthy controls at a group level [164]. Whereas patients with MSA demonstrated significant reductions in mean striatal, brainstem and cerebellar volumes, in patients with PSP significant reductions in whole brain, striatal, brainstem – especially midbrain – and frontal volumes have been shown [164]. By the application of stepwise discriminant analysis to MRV on a ROI basis, there was a good discrimination of patients with PD and controls from MSA and PSP patients. On the other hand, separation between patients with PD and controls as well as between MSA and PSP patients was insufficient (class II evidence) [185]. A similar approach, in which post-mortem-con-

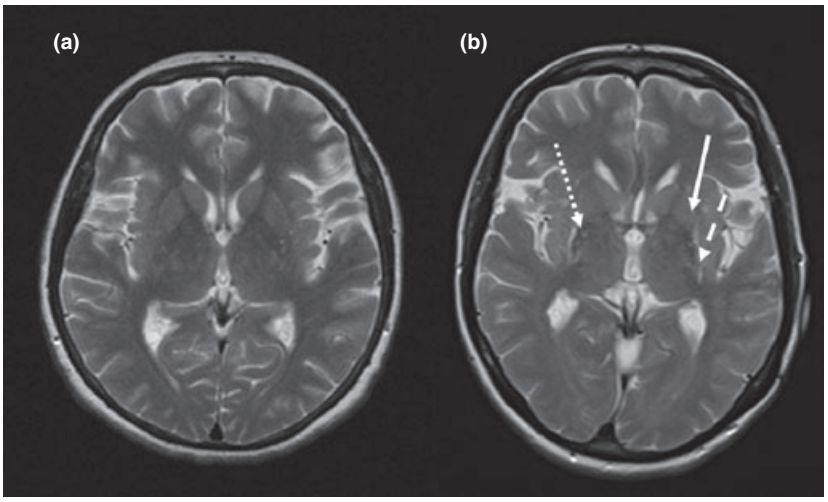

Figure 2 Axial T2-weighted MR images at the striatal level in a patient with Parkinson's disease (PD; image a) and a patient with MSA-P (image b). The image appears normal in the patient with PD (image a), whilst there are putaminal atrophy (arrow), putaminal hypointensity (dotted arrow) and a putaminal hyperintense rim (dashed arrow) in the patient with MSA-P (image b).

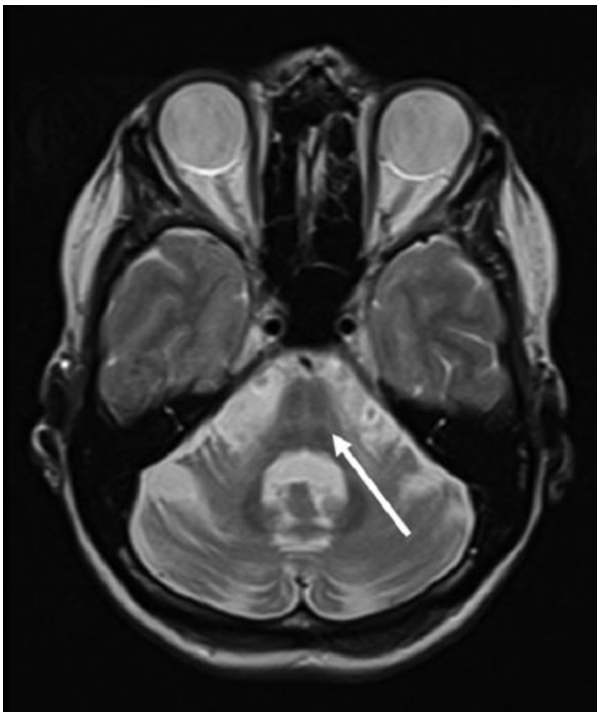

Figure 3 Axial T2-weighted MR image in a patient with MSA-P showing the 'hot cross bun' sign (arrow) in the basis pontis.

firmed cases of PSP and CBD were used to construct the model from the discriminant analysis, achieved a good diagnostic classification of patients with CBD and PSP as well as controls (class III evidence) [186]. Several studies suggest that MR planimetry represents a simple method for the differential diagnosis of neurodegenerative parkinsonism [164,179,187–191]. A decreased MCP width (<8 mm) seems to point the diagnosis towards MSA versus PD and controls (class II evidence) [188]. Studies comparing the MCP width between PSP and MSA patients do not exist. A reduced ratio between midbrain and pontine areas (class II evidence) [179,189] (class III evidence) [187,191] as well as an increased MR parkinsonism index (MRPI) (i.e. multiplying the ratio of pontine to midbrain area by the ratio of the MCP to SCP width) (class II evidence) [189] (class III evidence) [187,191] can point the diagnosis towards PSP versus PD, MSA and controls [164,179,187,189–191]. A reduced anterior –posterior (AP) midbrain diameter (<16 mm) was able to discriminate completely between PSP as well as patients with PD and controls in one study [190], whilst there was considerable overlap between patients with PD and patients with PSP using this marker in another study [183]. Also, there is overlap of AP midbrain diameter between PSP and MSA-P patients [171,190]. On the other hand, a midbrain AP cut-off of $\leq$14 mm seems to be very specific for PSP with variable sensitivity across the studies (class III evidence) [183,190]. Another study found that an AP midbrain diameter of <17 mm discriminated PSP from MSA-P (class III evidence) [171].

Voxel-based morphometry and voxel-based relaxometry have been used in neurodegenerative parkinsonism [2,164]. However, despite many advantages of voxel-based analysis (including its independency from operators due to automated detection), such technique is not at the moment appropriate for the routine use in individual patients, because it involves groupwise comparisons [164].

Several studies performed on a ROI basis could demonstrate that diffusion-weighted imaging (DWI) permits to differentiate early MSA-P from PD as well as healthy subjects on the basis of increased putaminal diffusivity in MSA-P [165,192–199] (Fig. 5). Putaminal diffusivity was also increased in PSP compared to PD, but with considerable overlap

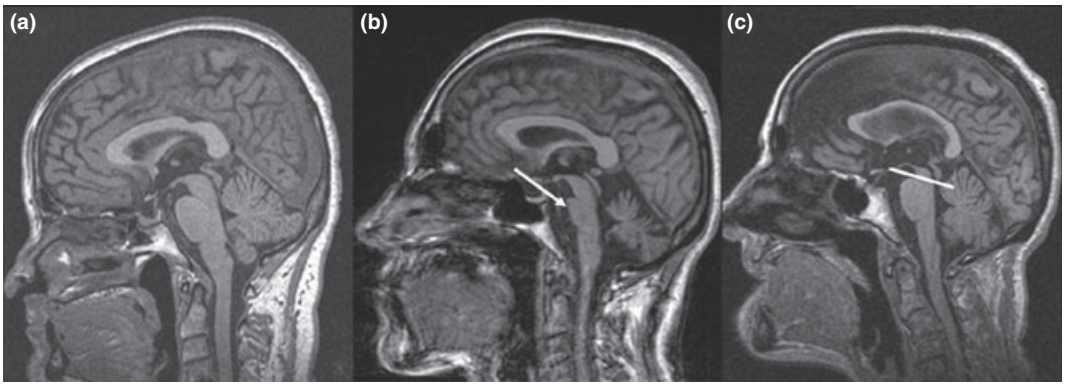

Figure 4 Midsagittal T1-weighted MR images in a patient with Parkinson's disease (PD; image a), a patient with MSA-P (image b) and a patient with progressive supranuclear palsy (PSP; image c). There is no pontine or midbrain atrophy in the patient with PD (image a). Image b demonstrates pontine atrophy (arrow) without midbrain atrophy in the MSA-P patient. Image c demonstrates the midbrain atrophy without pontine atrophy (divided by the white line) forming the silhouette of the 'penguin' or 'hummingbird' sign with the shapes of midbrain tegmentum (bird's head – above the white line) and pons (bird's body – below the white line) looking like the lateral view of a standing penguin (especially the king penguin) or hummingbird with a small head and big body.

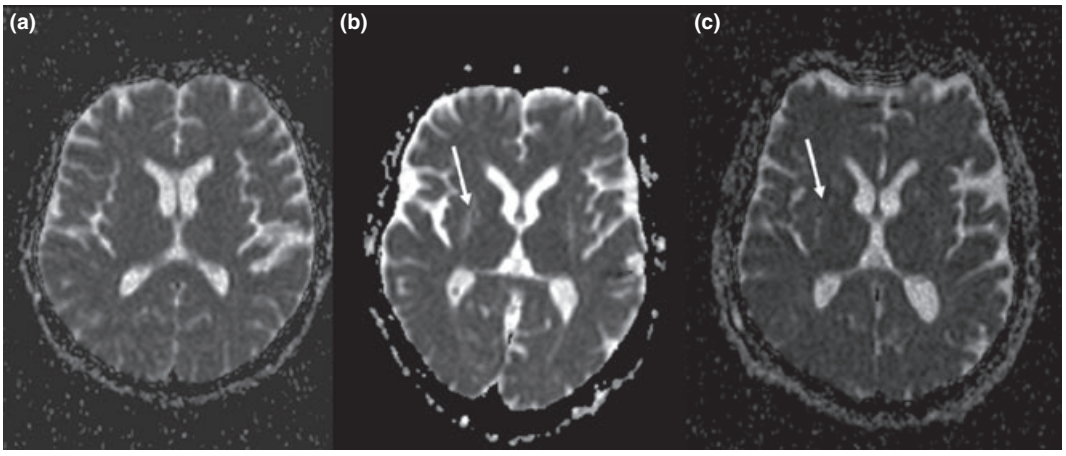

Figure 5 Axial Trace(D) maps at the level of mid-striatum in a patient with Parkinson's disease (PD) (image a), a patient with MSA-P (image b) and a patient with progressive supranuclear palsy (PSP) (image c). Note the diffuse hyperintensity – corresponding to increased diffusivity – in the putamen (arrows) in the patients with MSA-P (image b) and PSP (image c)

[193,196], so that increased putaminal diffusivity can point the diagnosis towards MSA-P versus PD and controls (class II evidence) [165,192–198] (class III evidence) [199], whilst frequencies of increased putaminal diffusivity in PSP vary across the studies (class II evidence) [193,196,200] (class III evidence) [199]. Although increased putaminal diffusivity overlapped in MSA-P and PSP patients, abnormal diffusivity measures in the MCP and SCP could respectively differentiate MSA from PSP [164]. Increased diffusivity in the MCP of MSA patients (including the MSA-P variant) has been reported to have a high diagnostic accuracy for MSA (and MSA-P) with respect to PSP, PD and controls in some publications (class II evidence) [196,200]. However, there was a considerable overlap between MCP diffusivity in patients with MSA-P versus patients with PSP, PD and controls in another study and similar MCP diffusivity values in patients with MSA-P and controls (class II evidence) [198,201]. Further studies are warranted to clarify this issue. Increased diffusivity in the SCP has been reported in patients with PSP compared to patients with PD, MSA-P and controls, (class II evidence) [201,202] (class III evidence) [199], so that increased diffusivity in the SCP can point the diagnosis towards PSP versus PD, MSA-P and controls. One study with methodological concerns [164] failed to detect diffusivity changes in the putamen in patients with MSA-P and PSP as well as in the SCP in patients with PSP (class II evidence) [200]. Similar

to PSP, CBD patients seem to display higher diffusivity in the SCP compared to patients with PD and controls, thus not allowing to differentiate PSP and CBD on the basis of diffusivity changes in the SCP (class III evidence) [199]. The same study showed similarly higher putaminal diffusivity in CBD and PSP patients with respect to PD ones and controls, allowing discrimination of these APS from idiopathic PD and controls [199]. However, complete discrimination between CBD and the other groups including PSP was only reached by applying a hemispheric symmetry ratio (i.e. smaller to the larger median value of ADC histograms of left and right hemispheres) [199]. Using 3.0-T MRI, diffusivity in the pons, cerebellum and putamen was significantly higher and coupled with significantly lower fractional anisotropy (FA) values in the same regions, in MSA compared to PD and controls. All patients who had both significantly low FA and high diffusivity in each of these three areas were MSA-P cases, and those that had both normal FA and Trace(D) values in the pons were all PD cases (class II evidence) [203].

In PD, newer quantitative imaging techniques implemented on 3-T systems (see Table 3) have shown promising results in detecting abnormalities in the SN and nigrostriatal pathways [204–207] with high diagnostic accuracy in separating PD patients from healthy controls (class II evidence) [204–207]. These findings warrant further confirmatory studies.

Recommendations

We conclude that cMRI at 1.5 T is principally helpful to exclude symptomatic parkinsonism due to other pathologies (Level B).

1.5-T cMRI is also useful in the differentiation of PD from APS as follows:

I) MSA signs – Putaminal atrophy and rim sign, pontocerebellar atrophy, MCP hyperintensity and hot cross bun sign (all Level A);

II) PSP signs – Midbrain atrophy and hummingbird sign (both Level B), SCP atrophy (Level C).

Specificity of these abnormalities to differentiate APS from PD is considered quite high, whereas sensitivity, particularly in early disease stages, seems to be insufficient. A normal routine 1.5-T cMRI does not exclude MSA or PSP, if the clinical presentation is suggestive and supported by the current diagnostic criteria.

Abnormalities on DWI at 1.5 T including diffusivity changes in

I) Putamen in patients with APS versus PD in early disease stages (especially MSA-P, Level A)

II) SCP in patients with PSP (Level B) have been described as markers, which can point the diagnosis towards MSA or PSP instead of PD.

Newer quantitative imaging techniques implemented on 3-T systems have shown promising results. However, they require further confirmatory studies.

Single photon emission tomography

Single photon emission tomography (SPECT) with selective radioligands for striatal dopaminergic nerve terminals allows an objective and reproducible measurement of the nigrostriatal dopaminergic system. Available pre-synaptic radioligands selectively target the dopamine transporter (DAT), making this a biomarker of diseases involving the nigrostriatal pathway (class II evidence) [209]. All successful DAT-binding agents belong to a group of tropane derivatives, which share a similar backbone structure with cocaine. The first successful DAT imaging agent for SPECT was [^{123}I]β-CIT, and the results reported in the early 1990s suggested a strong correlation between putaminal abnormalities and clinical symptoms of PD (class II evidence) [210]. Over time, several other tracers have been developed for this purpose. In recent years, [^{123}I] fluopane (FP)-CIT was first registered in Europe (and later also in the USA) for the early diagnosis of parkinsonism and in the differential diagnosis from essential tremor (class I evidence) [211] (Fig. 6).

Dopamine transporter-SPECT cannot differentiate PD from APS (e.g. MSA or PSP) (class III evidence) [212], given a similar nigrostriatal involvement in these diseases. However, using an observer-independent software for statistical parametric mapping, reduced midbrain [^{123}I]β-CIT uptake was found in patients with MSA-P and allowed a correct classification of 95% patients suffering from MSA-P or PD, respectively (class II evidence) [213]. DaTscan SPECT proves also useful in suspected neuroleptic-induced parkinsonism, as it can separate purely drug-induced cases (normal uptake) from those with concomitant dopaminergic degeneration (class II evidence) [214].

SPECT imaging of dopamine D2 receptors has no clinical value in confirming the diagnosis of PD. The main clinical application for post-synaptic SPECT imaging is the differential diagnosis of PD from APS. Nevertheless, [^{123}I] IBZM SPECT cannot itself discriminate amongst different APS (class III evidence) [212].

Cerebral blood flow (CBF) and SPECT investigations may potentially clarify the neural substrates of motor and cognitive symptoms, as well as chronic

Table 3 Findings with quantitative imaging techniques implemented on 3-T MR systems in PD

Author, year (reference)	Cohort size (mean age, mean disease duration, range disease duration)/design	MRI Methodology	Marker	Sensitivity (%)	Specificity (%)
Vaillancourt 2009 [204]	• PD 14 de novo untreated with H&Y 1-2 (57y, 16m, 433 m)/controls 14 (58y) • Prospective blinded analysis	DTI of the SN (subregions)	Decreased FA in caudal SN	100	100
			Decreased FA in middle SN	100	35
			Decreased FA in rostral SN	100	7
Menke 2009 [205]	• PD 10 with H&Y 1–3 (64y, 6y, 1–14y)/controls 10 (64y) • Prospective blinded analysis	Combined SN volumetry with DTI of SN ([a]VCDR)	Decreased SN volume	80	70
			Decreased VCDR[b]	100	70
			Decreased SN volume + decreased VCDR	100	80
Gröger 2011 [206]	• PD 9 with H&Y 2,5–3, all medicated (69y, n.g., 4–25y)/controls 8 (66y) • Prospective blinded analysis	3D-MRSI of the SN	Decreased NAA/Cr ratio of rostral SN	89	50
			Increased NAA/Cr ratio of caudal SN	89	75
			Decreased rostral-to-caudal ratios of the NAA/Cr ratio	100	100
Peran 2010 [207]	• PD 30 with H&Y 1–2, all medicated (62y, 4.5y, n.g.)/controls 22 (57y) • Prospective blinded analysis	Multimodal study using a combination of different MR markers including volumetry, mean R [b], mean diffusivity and FA applied in 6 deep grey matter structures (SN, RN thalamus, putamen, caudate and pallidum)	Increased R2[b] in the substantia nigra, reduced FA in the substantia nigra and increased mean diffusivity in the putamen or caudate nucleus	Discriminant power[c]: • 71–83% in considering only one marker • 95–98% in considering the three-marker combinations	
Melzer 2011 [208]	• PD 61 with 26 drug-naïve (cognitively normal n = 34: 65y, 3y; with mild cognitive impairment n = 16: 70y, 9y; with dementia, n = 11: 75y, 12y)/controls 29 (69y) • Prospective blinded analysis	Perfusion imaging study with arterial spin labelling	PD-related perfusion network by principal component analysis	AUC of ROC[2]: • Controls versus PD 0.71 • Controls versus PD + MCI 0.94 • Controls versus PDD 0.99 • De novo patients not analysed	

PD, Parkinson's disease; PDD, PD dementia; SN, substantia nigra; RN, red nucleus; DTI, diffusion tensor imaging; 3D-MRSI, three-dimensional magnetic resonance spectroscopic imaging; R2[b], relaxation rates = 1/T2[b]); FA, fractional anisotropy; ASL, arterial spin labelling; AUC, area under the curve; ROC, receiver operating characteristic analysis; n.g. not given.

[a]VCDR is a DTI marker representing the numbers of voxels for all connectivity-defined subregions within the SN thresholded at 10% of the maximum connection probability.

[b]Reduced left and right SN to ipsilateral thalamus VCDRs.

[c]Sensitivity, specificity not given.

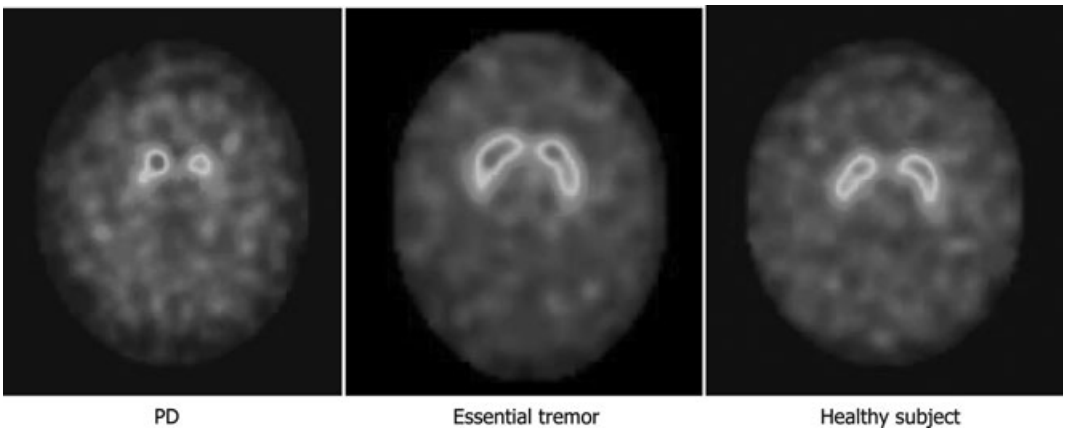

Figure 6 Dopamine transporter SCAN imaging of a patient with Parkinson's disease (PD), an essential tremor patient and an healthy subject. Courtesy of Eveline Donnemiller, Department of Nuclear Medicine, Medical University Innsbruck.

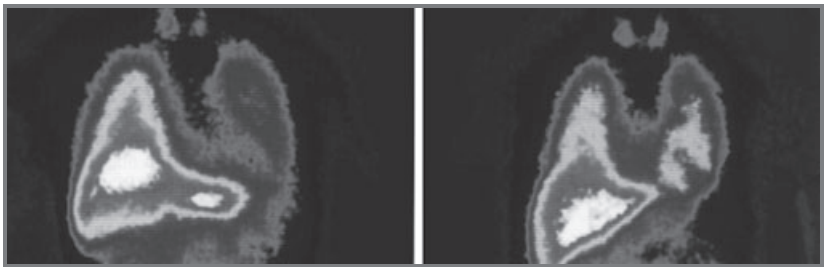

Figure 7 Metaiodobenzylguanidine (MIBG) uptake in Parkinson's disease (PD) (left) and multiple system atrophy (MSA) (right). Please note normal heart uptake in the MSA patient. The structure showing extensive uptake in both patients is the liver.

medication effects in PD (class III evidence) [215]. Specific CBF decrements have been shown in PDD patients (mostly in the parietal and occipital cortex class III evidence) [216], PSP (mostly frontal lobe) as well as MSA (striatum, class II evidence) [217].

Interest has recently developed also on the use of MIBG, an analogue of norepinephrine. MIBG can be labelled with ^{131}I ([^{123}I] MIBG). MIBG is actively uptaken from cardiac adrenergic fibres by the sodium- and energy-dependent human norepinephrine transporter. It is afterwards secreted after cholinergic pre-ganglionic stimulation. Thus, [^{123}I] MIBG traces not only the localization, but also the functional integrity of catecholaminergic nerve endings.

Atypical parkinsonian syndromes and vascular parkinsonism usually show normal or only mild reduction in cardiac [^{123}I] MIBG uptake in contrast with PD, where [^{123}I] MIBG uptake is significantly reduced or absent (class II evidence; Fig. 7) [218]. The main drawback of [^{123}I] MIBG/SPECT is a low specificity (37.4%), whilst its sensitivity is relatively high (87.7%) (class II evidence) [219]. One study directly compared [^{123}I] MIBG with [^{123}I]FP-CIT in PD subjects (Hoehn and Yahr stage 1) showing higher sensitivity for [^{123}I]FP-CIT (83% vs. 72%) (class II evidence) [220].

Recommendations

DaTscan-SPECT is registered in Europe and the United States for the differential diagnosis between degenerative parkinsonism and essential tremor (Level A). More specifically, DaTscan SPECT is indicated in the presence of significant diagnostic uncertainty and particularly in patients presenting atypical tremor manifestations. Cardiac [^{123}I] MIBG/SPECT imaging may assist in the differential diagnosis of PD versus APS (Level A).

All other SPECT imaging studies do not fulfil registration standards and cannot be recommended for routine clinical use.

Positron emission tomography

Positron emission tomography (PET) has been used in two main ways to support a diagnosis of PD. The first is via detection of striatal dopamine deficiency (SDD) state associated with degenerative parkinsonian syndromes including PD, MSA, PSP and CBD and differentiating these latter from essential and dystonic tremors, drug-induced and psychogenic parkinsonism [221]. Tracers useful for this purpose include ^{18}F-dopa – a marker of dopa decarboxylase activity in the

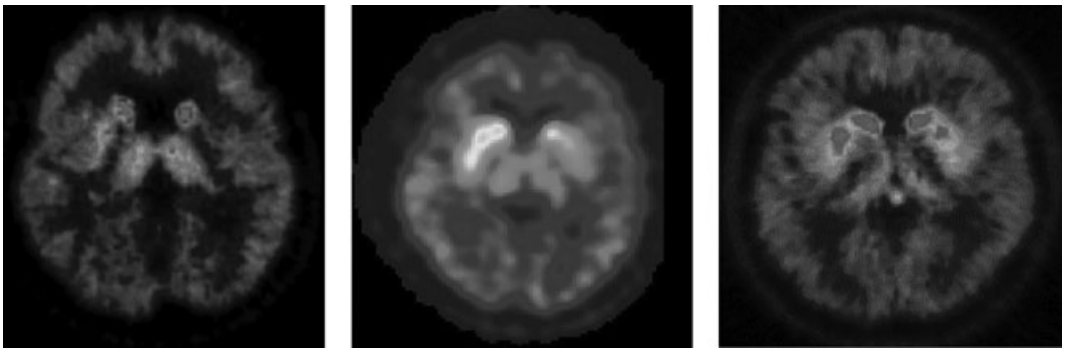

Figure 8 Images of striatal ^{11}C-RTI-32 positron emission tomography (PET) dopamine transporter (DAT), ^{11}C-DTBZ PET (VMAT2) and ^{18}F-dopa PET (dopa decarboxylase) uptake in healthy volunteers and early Parkinson's disease (PD). It can be seen that the three PET imaging modalities all show asymmetrically reduced posterior putamen dopaminergic function in PD.

dopaminergic terminal [222], ^{11}C- and ^{18}F-dihydrotetrabenazine (DTBZ) – both markers of monoamine vesicular transporter binding [223,224], and ^{11}C-methylphenidate [225], ^{18}F-CFT [226], ^{11}C-RTI-32 [227] [7] and ^{18}F-FP-CIT [228] – all markers of DAT availability (Fig. 8). It has been demonstrated that levels of SDD correlate well with locomotor disability [229] and progression of disease can be detected in longitudinal studies [226,230,231]. Additionally, pre-motor SDD can be detected in some adult subjects at risk for PD, such as LRRK2 gene carriers [232], asymptomatic relatives of familial PD cases [233] and homozygous twins [234].

Whilst these PET tracers have high sensitivity for detecting SDD, they do not reliably discriminate between parkinsonian syndromes, although PD is associated with a rostro-caudal putamen gradient of dopamine dysfunction compared with the more uniform dysfunction evident in PSP and CBD [235]. In PD, putamen dopamine D2 receptor availability is preserved or even mildly increased in de novo cases. This can be demonstrated with PET benzamide tracers such as ^{11}C-raclopride [236]. In contrast, striatal D2 binding is reduced in MSA, PSP and CBD, although significant decreases are only present in around 50% of individuals [237,238].

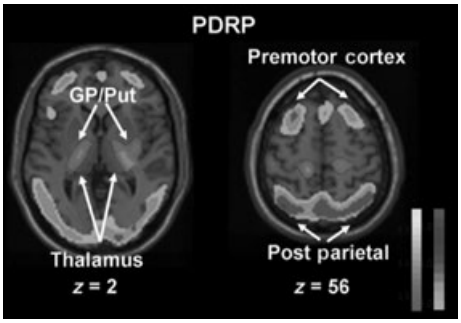

Figure 9 Covariance analysis of FDG positron emission tomography (PET) showing the Parkinson's disease (PD)-related profile of raised lentiform and reduced frontal metabolism (Eidelberg 1990).

The second approach involves ^{18}F-FDG PET which allows the patterns of resting brain glucose metabolism (rCMRGlc) to be determined. In PD, covariance analysis reveals a characteristic profile where lentiform rCMRGlc is relatively increased and frontal rCMRGlc lowered. This has been indicated as the PD-related profile (PDRP; Fig. 9) [239]. The PDRP correlates with locomotor disability when patients are temporarily withdrawn from medication and can be normalized by the treatment with dopaminergic agents [240]. In contrast, APS characteristically show reduced striatal rCMRGlc and can be sensitively discriminated from typical PD [241]. It may also be possible to discriminate between the atypical syndromes by the patterns of brainstem and cortical involvement [242].

In summary, PET imaging cannot directly diagnose PD or APS. The patterns of dysfunction it reveals can help supporting or refuting clinical impressions. If neuroprotective or restorative therapies become available, PET can also reveal subclinical dysfunction in at-risk subjects for PD.

Recommendations

None of the reviewed PET studies has been performed according to regulatory standards with the exception of the study by Whone *et al*. [230]. Therefore, we cannot make any formal recommendation for the routine use of PET studies in the diagnostic work-up of PD.

Table 4 Tools for the diagnosis of Parkinson's disease. Recommendations of the EFNS/MDS-ES Task Force

Section	Recommendation level	Notes
1. Clinical Diagnostic Criteria		
1.1 QSBB clinical diagnostic criteria	B	Some *exclusion* and *supportive* criteria deserve future revision
2. Genetic Testing		
2.1 *SNCA* gene point mutations and multiplication	B	To be screened in PD families suggestive of dominant inheritance
2.2 *LRRK2*, known pathogenic variants	B	To be screened in: I. Typical PD cases with family history suggestive of dominant inheritance II. In sporadic PD cases from specific populations with known founder effect mutations
2.3 *GBA* mutations	B	Founder effect mutations to be searched in PD cases from specific populations (i.e. Ashkenazi Jewish) with or without positive family
2.4 *parkin, PINK1, DJ-1* mutations	B	To be screened in: I. PD cases with disease onset <50 years of age and family history suggestive of recessive inheritance II. Sporadic PD cases with disease onset <40 years of age
2.5 *ATP13A2, PLA2G6, FBX07*	B	To be screened in very-early-onset PD cases with negative *parkin, PINK1, DJ-1 testing*
3. Autonomic function testing	Insufficient evidence	
4. Olfactory tests (UPSIT, Smell Test)		
4.1 PD versus atypical and secondary parkinsonism	A	
4.2 Idiopathic PD versus recessive PD forms	A	
4.3 Pre-motor PD	A	To be used in conjunction with other screening tests
5. Drug Challenge Test (L-Dopa, Apomorphine)		
5.1 Diagnosis of de novo parkinsonian patients	Not recommended	
5.2 Differential diagnosis between PD and atypical parkinsonism	Insufficient evidence	
6. Neurophysiological tests		
6.1 EEG	Insufficient evidence	
6.2 Evoked Potentials	Insufficient evidence	
6.3 Sleep studies	Insufficient evidence	
6.4 Tremor analysis	Insufficient evidence	
6.5 EMG/ENG	Insufficient evidence	
7. Neuropsychological tests		
7.1 Initial evaluation of a suspected PD case	A	Evaluation should include: I. Collateral history from a carer II. Brief assessment of cognition screening for RBD, psychosis, severe depression
8. Neuroimaging		
8.1 Transcranial Sonography		
8.1.1 Differential diagnosis of PD from atypical and secondary parkinsonism	A	
8.1.2 Early diagnosis of PD	A	
8.1.3 Detection of subjects at risk for PD	A	To be used in conjunction with other screening tests
8.2 Magnetic Resonance Imaging (MRI)		
8.2.1 Conventional 1,5-T MRI-Differential diagnosis of MSA from PD: Putaminal atrophy Rim sign Pontocerebellar atrophy Middle cerebellar peduncle hyperintensity 'Hot cross bun' sign	A	

Table 4 (*Continued*)

Section	Recommendation level	Notes
8.2.2 Conventional 1,5-T MRI-Differential diagnosis of PSP from PD: Midbrain atrophy Hummingbird sign	B	
8.2.3 Conventional 1,5-T MRI-Differential diagnosis of PSP from PD: Superior cerebellar peduncle atrophy	C	
8.2.4 1,5-T DWI-Differential diagnosis of MSA from PD: Putaminal diffusivity changes	A	
8.2.5 1,5-T DWI-Differential diagnosis of PSP from PD: Superior cerebellar peduncle diffusivity changes	B	
8.3 Single Photon Emission Tomography (SPECT)		
8.3.1 DAT Scan-Differential diagnosis of Essential Tremor from PD and atypical parkinsonism	A	Cost-effective investigation
8.3.2 ^{123}I-MIBG SPECT-Differential diagnosis of PD from MSA-P and controls	A	
8.4 Positron Emission Tomography (PET)	Insufficient evidence	

DAT, dopamine transporter; DWI, diffusion-weighted imaging; MIBG, metaiodobenzylguanidine; MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; QSBB, Queen Square Brain Bank; RBD, REM sleep behaviour disorder.

Section 9: economic issues

Cost-effectiveness data are scarce in PD. Only ^{123}I-FP-CIT SPECT was assessed in three jurisdictions (Italy [243], Belgium [244] and Germany [245]). In all three publications, the authors came to the conclusion that ^{123}I-FP-CIT SPECT has to be regarded as cost-effective investigation for the differential diagnosis of essential tremor from parkinsonian disorders, if used as a confirmatory test in drug-naïve patients with a positive clinical examination. There are insufficient cost-effectiveness data for all the other diagnostic modalities reviewed in this statement. This is an area of unmet need deserving future investigations.

Recommendations

None.

Concluding remarks

The correct diagnosis of PD is important for prognostic and therapeutic reasons and is essential for clinical research. Increasing knowledge of the heterogeneous clinical presentation of parkinsonian syndromes has resulted in improved diagnostic accuracy. Recommendations of the EFNS/MDS-ES for the diagnosis of PD are summarized in Table 4. As to clinical diagnostic criteria, only the QSBB criteria have been fully validated, reaching class III evidence and a Level B recommendation. Genetic testing, ranking a Level B recommendation, should be performed according to the clinical presentation including age at disease onset. It may identify a hereditary cause in parkinsonian subjects with a positive family history. Olfactory testing is a cheap and extensively validated tool that contributes to the early diagnosis of PD and also to its differential diagnosis (Level A). Recent evidence suggests that it may also serve as screening tool to identify patients with pre-motor PD. TCS of the SN is recommended for the early diagnosis of PD and its differential diagnosis from atypical parkinsonism (Level A). It may serve as screening tool for at-risk individuals in conjunction with other screening tests as well (Level A). Neuropsychological testing, functional and structural neuroimaging investigations should be primarily performed to exclude other causes of parkinsonism in patients with suspected PD (Level A). Further studies are needed for autonomic, drug challenge, neurophysiological testing and PET imaging in order to establish their role in the diagnosis of PD.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Clinical Diagnostic Criteria for Parkinson's Disease.

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