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Diagnosis and Differential Diagnosis of Parkinson’s Disease

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1. Introduction

Parkinsonian syndromes are a heterogeneous entity of movement disorders, which can be subdivided into idiopathic Parkinson’s disease, rare genetic forms of Parkinson’s disease as well as symptomatic and atypical parkinsonian syndromes. In addition, a number of other neurodegenerative disorders may show clinical signs of Parkinsonism. The etiology, histopathology, clinical manifestation and disease course varies significantly among these disorders. A correct and early differential diagnosis therefore is essential for proper prognostic estimation and consultancy of the patient as well as a prerequisite for inclusion in clinical studies.

This chapter will summarize diagnostic criteria mainly focussing on the diagnosis of idiopathic Parkinson’s disease (iPD) and delineate specific factors to differentiate this disorder from other disease entities.

2. Clinical signs

Idiopathic Parkinson’s disease is a progressive, neurodegenerative movement disorder, which in its most classical manifestation is characterized by the triad of bradykinesia, muscular rigidity and tremor. iPD is the most frequent neurodegenerative movement disorder with a mean prevalence of ~150/100.000 (Errea et al., 1999; Walker et al., 2010). A definite diagnosis has to be based on histopathological analysis and requires cell loss in the substantia nigra, the presence of Lewy bodies, which stain for alpha-synuclein and ubiquitin, and usually can be obtained only post mortem. In addition, the histology has to exclude histopathological features of other disorders, which could mimick clinical PD, such as atypical parkinsonian syndromes (Gelb et al., 1999). While these criteria are useful for post mortem classification, several attempts have been made to define clinical diagnostic criteria, e.g. by the UK Parkinson’s Disease Society Brain Bank (UKPDSBB) (Hughes et al., 1992) or the National Institute of Neurological Disorders and Stroke (NINDS) (Gelb et al., 1999). For clinical practice, the implementation of modified UKPDSBB criteria has proven useful: here, the diagnosis is based on (1) the identification of parkinsonian symptoms, (2) the absence of exclusion criteria and (3) the presence of prospective positive criteria (Table 1). However, it has to be kept in mind, that even if these criteria are verified by expert
neurologists, the diagnostic certainty is only between 75 - 90 % when compared with the results of the autopsy (Hughes et al., 2001; Dickson et al., 2009).

**Step 1 Diagnosis of Parkinsonian syndrome**
- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- and at least one of the following:
  - muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

**Step 2 Exclusion criteria for idiopathic Parkinson’s disease**
- Repeated strokes with stepwise progression of parkinsonian features
- 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 cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

**Step 3 Supportive prospective positive criteria for idiopathic Parkinson’s disease** (Three or more required for diagnosis of definite Parkinson’s disease)
- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Table 1. UK Parkinson’s Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria for idiopathic Parkinson’s disease (from Hughes et al., 1992).

Although numerous supplementary technical exams are available, which may increase diagnostic certainty, the initial diagnosis remains a clinical one and can be based purely on medical history and clinical examination. Motor symptoms in iPD are clinically most striking, but a number of less prominent non-motor symptoms may already be present at
onset. These non-motor symptoms (such as olfactory dysfunction or altered sleep behaviour) have not yet been sufficiently recognized in structured diagnostic criteria, but are likely to be included in the future. The importance of non-motor symptoms is further underlined by recent studies suggesting a premotor phase ranging from 5 – 20 years before the onset of motor symptoms (Savica et al., 2010). Even more importantly, when patients were asked about the impact of symptoms on health-related quality of life autonomic dysfunction, psychiatric complications, pain, fatigue, and sleep problems were mainly correlated with a negative impact (Gallagher et al., 2010).

IPD has been observed in all age groups, but about 75 % of all cases show first motor symptoms after an age of 60. Age is the single most consistent risk factor for developing iPD and should be considered in the differential diagnosis (Hindle, 2010). Only ~ 5 % of all PD cases begin before the age of 40 and these are likely to be caused by genetic mutations (Wickremaratchi et al., 2009).

2.1 Motor symptoms

The initial presentation may vary, with tremor being the most common motor symptom in patients, in which the diagnosis of iPD has been verified post-mortem (Hughes et al., 1993). A recent community-based study in 358 patients identified tremor as initially leading symptom in approximately half of the patients. Some 44 % showed an akinetic-rigid phenotype and only 7 % presented with a leading gait disturbance. Interestingly, the akinetic-rigid presentation was more pronounced in younger patients, while tremor and gait disturbance as initial symptoms increase with the age at presentation (Wickremaratchi et al., 2011).

2.1.1 Bradykinesia

Slowness of initiation and execution of voluntary movements, such as limb movements, facial expression or gait, characterizes bradykinesia. Diadochokinesis (the ability to perform rapid alternating movements) is usually slowed (Haaxma et al., 2010). Micrographia with a characteristic decrease of character size towards the end of the line, the shuffling gait with a diminished gait quadrangle and reduced arm swing, and hypomimia with a progressive loss of facial expression are classical manifestations of bradykinesia. Because of the severe hypomimia with a lack to adequately support emotional expression, PD patients may wrongly be considered depressive. At the same time, one has to keep in mind that depression is a common concomitant disorder, which may occur in up to ~ 20 % of PD patients (Brown et al., 2011).

2.1.2 Tremor

The characteristic tremor is a low-frequency (4-6 Hz) resting tremor, but other tremor forms, such as an action tremor or a postural tremor may occur as the disease progresses (Jankovic et al., 1999). Other tremor entities, most importantly essential tremor (ET), have to be considered in the differential diagnosis and tremor frequency is a major differentiation criterion (see part 4.4). Therefore, a tremor analysis may be a helpful additional examination to quantify the characteristics of the tremor presented. There is evidence to suggest that there is an association and even histopathological overlap in some cases of ET and iPD, but the case is not yet closed on this issue (Raethjen and Deuschl, 2009). Like most symptoms in iPD, the tremor manifests with a unilateral preference. In the course of the disease, tremor intensity may diminish and give way to the bradykinetic symptoms. Very importantly one has to note, that about one of four of all iPD patients does not develop a characteristic tremor during the entire course of the disease (Hughes et al., 1993).
2.1.3 Rigidity
Rigidity becomes apparent at the clinical examination, when the passive movement of a limb is impaired by a wax-like resistance. In combination with the tremor frequency this results in the cogwheel phenomenon upon passive movement in a joint. Many patients with iPD initially complain of unilateral back and/or shoulder pain as a consequence of the asymmetric muscular tone, which may result in the consultation of an orthopedic specialist before final referral to a neurologist (Madden and Hall, 2010).

2.1.4 Postural instability
Postural instability regularly appears in the course of the disease, most often in more advanced stages (Coelho et al., 2010). In progressive disease it may be considered as important diagnostic feature and supports the initial diagnosis (Hughes et al., 1992). However, pronounced postural instability at the initial presentation may be an indicator for progressive supranuclear palsy (PSP) instead of iPD (Litvan et al., 1996) and therefore has to be carefully set into context with other motor features.

Usually the motor symptoms are asymmetrically distributed and in cases with a strict bilateral presentation one should consider the differential diagnosis of a symptomatic or atypical parkinsonian syndrome.

2.2 Non-motor symptoms
Since the landmark studies of Braak and colleagues the picture of iPD as a mainly nigrostriatal disorder is no longer sustainable. In fact, these analyses suggest that the pathoanatomical changes, such as the presence of Lewy bodies and Lewy neurites appear first in the medulla oblongata, the pons and the olfactory bulb, then spread to the midbrain and lastly affect the neocortex (Braak et al., 2003). It is no surprise thus, that symptoms deriving from dysfunction of these brain regions may precede motor symptoms and other non-motor symptoms may develop in late stage disease.

2.2.1 Olfactory dysfunction
Olfactory dysfunction has been recognized to be an early clinical sign in patients with iPD and bedside testing can be easily performed by standardized odour test batteries (see part 3.3.1). Approximately 70 - 90 % of all iPD patients present with a significant lack of odour discrimination and it seems to be present well before the onset of motor symptoms (Doty et al., 1988; Kranick and Duda, 2008), which could result in a future use of olfactory testing in combination with other parameters as a biomarker in putative neuroprotective therapies. A recent study evaluating brain glucose metabolism suggests that hyposmia is related to cognitive impairment due to cortical dysfunction in iPD patients and that the cognitive deficit in olfactory perception is at least partially responsible for diminished smell differentiation. Altered metabolism in the amygdala and the piriform cortex could be responsible for this sensory deficiency (Baba et al., 2011).

2.2.2 Dysautonomia
Dysautonomic features, such as seborrhoea, orthostatic hypotension, gastrointestinal or urinary dysfunction may occur before or after the onset of motor symptoms (Bassetti, 2010). Their early presence (especially urinary dysfunction, orthostatic hypotension) should however always challenge the diagnosis of iPD and lead to consideration of the differential diagnosis of atypical parkinsonian syndromes, such as multisystem atrophy (MSA) or progressive supranuclear palsy (PSP) (Colosimo et al., 2010).

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Urinary dysfunction is especially debilitating for the patient and usually manifests as overactive bladder syndrome, which has been attributed to the degeneration of central serotonergic projections. It correlates with disease severity (measured by the UPDRS-III score) and patient age (Iacovelli et al., 2010).

Gastrointestinal symptoms are present in more than half of iPD patients and may comprise constipation, dysphagia, nausea, vomiting, incomplete bowel emptying or incontinence. As for other dysautonomic symptoms, the prevalence in atypical parkinsonian syndromes, such as MSA or PSP, but also in DLB is much higher (Colosimo et al., 2010).

Symptomatic postural hypotension is less frequent in iPD, but ~20 % of the patients show a drop in systolic blood pressure of more than 20 mmHg associated with postural events (Senard et al., 1997). If orthostatic hypotension is prominent at initial presentation, the diagnosis of MSA should be considered.

While above-mentioned symptoms are likely to be verbalized by the patients, sexual dysfunction is not. Patients may not even be aware of the fact that erectile dysfunction and loss of libido are part of the non-motor symptom complex observed in iPD and these symptoms are therefore likely to be underreported. Nevertheless, a recent study analyzing the most bothersome symptoms reported by iPD patients in early stage disease (up to 6 years disease duration) listed sexual dysfunction at place 12 of 24 and this was similar in late stage disease patients (Politis et al., 2010).

2.2.3 Depression and anxiety

Neuropsychiatric disorders, such as depression and anxiety are frequently found alongside with motor symptoms - approximately 40 % of all iPD patients show anxiety-related, depressive or combined psychopathology (Brown et al., 2011). A recently published analysis demonstrates a positive correlation between depression and higher UPDRS/Hoehn and Yahr stages. Also, other non-motor symptoms, such as anxiety, hallucinations and sleep disturbances were more frequently observed in depressed iPD patients (Dissanayaka et al., 2011). Disease severity in iPD has also been shown to be positively correlated with anxiety and patients with young onset, gait dysfunction and postural instability were especially prone to develop an anxiety disorder (Dissanayaka et al., 2010).

2.2.4 Cognitive decline and dementia

About 40 % of all patients initially diagnosed with iPD will develop cognitive decline with dementia in the course of the disease (Aarsland et al., 2001). According to the current diagnostic criteria, the occurrence of cognitive dysfunction in patients with parkinsonian symptoms later than 12 months after the first presentation of motor symptoms is considered as Parkinson's disease dementia. When cognitive decline occurs before or within the first year of motor symptom onset, dementia with Lewy-bodies (DLB) has to be diagnosed rather than iPD (McKeith et al., 1996). Because of their histopathological similarities, it is likely that iPD and DLB are not separate entities, but different manifestations within the spectrum of disorders, which are defined by the presence of pathologic alpha-synuclein aggregates, so-called alpha-synucleinopathies. The neuropsychological examination for Parkinson's disease dementia should include specific scales which should be powered to detect cortical dysfunction. For example, the Scales for Outcomes of Parkinson's disease-Cognition (SCOPA-COG), Parkinson's Disease-Cognitive Rating Scale (PD-CRS), and Parkinson Neuropsychometric Dementia Assessment (PANDA) are likely to yield a more precise assessment of the patient's cognitive dysfunction than general dementia assessments (Kulisevsky and Pagonabarraga, 2009).
2.2.5 REM-sleep behaviour disorder
REM-sleep behaviour disorder (RBD) is an especially interesting feature of iPD patients, because it can appear many years before the diagnosis of the disease based on classical motor symptoms (Claassen et al., 2010) and is observed in up to 25 % of all iPD patients (Gjerstad et al., 2008 JNNP). RBD is characterized by increased motor activity during REM sleep, which may result in vocalization and vigorous limb movements. Patients usually also describe a vivid and sometimes terrifying dreaming experience. Sleep disturbances as well as restless legs are ranked high in the list of most bothersome symptoms for early and even more late stage iPD patients (Politis et al., 2010). In addition, up to 50 % of iPD patients complain of excessive daytime sleepiness, which also can precede the manifestation of motor symptoms by many years (Abbott et al., 2005).

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<td>- REM sleep behavior disorder and insomnia</td>
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Table 2. Non-motor features which may occur in idiopathic Parkinson’s disease.

3. Additional exams

Although the diagnosis of iPD can be made based purely on clinical examination, additional technical exams can help to differentiate other degenerative disorders, most importantly secondary or atypical parkinsonian syndromes.

3.1 Imaging approaches
3.1.1 MRI
There are currently no MRI-criteria in clinical use for the verification of a putative iPD diagnosis. No single morphological marker could be identified permitting the diagnosis of iPD, even though several parameters exist, which help to differentiate iPD from atypical parkinsonian syndromes. Recent approaches combining different magnetic resonance parameters (such as R2* value, mean diffusivity and fractional anisotropy) have been shown to achieve a high accuracy for the discrimination of iPD patients and controls (Péran et al.,

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Diagnosis and Differential Diagnosis of Parkinson’s Disease (2010). It remains to be seen whether similar techniques find application in the clinical practice and whether they will be able to separate other entities from iPD. Nevertheless, conventional CT and MRI imaging has its place in the diagnostic workup for suspected iPD and is widely used to exclude common differential diagnoses, such as vascular PD, Wilson’s disease, or atypical parkinsonian syndromes (see section 4).

3.1.2 SPECT imaging
Imaging with radiolabeled ligands has markedly improved the functional diagnostics of Parkinson’s disease. PET and SPECT techniques permit to visualize the pre- and postsynaptic compartment of the nigrostriatal projections and thus draw a semiquantitative picture about functionality of these pathways. In clinical use, they are mostly used for the differentiation of iPD from atypical parkinsonian syndromes or from essential tremor (ET).

The dopaminergic deficit can be quantified by a DAT-SPECT (DaTSCAN®) using $^{123}$I-FP-CIT and is a measure for the presynaptic dopamine transporter in the striatal dopaminergic synapse (Booij et al., 1997). The DaTSCAN should be used, if the dopaminergic deficit itself is clinically unclear, i.e. too subtle, or if tremor is the prominent symptom, which makes the discrimination between iPD and ET difficult (Benamer et al., 2000). The DaTSCAN also correlates with the rate of dopaminergic degeneration in the course of the disease (Winogrodzka et al., 2001) and, similarly to the clinical presentation, the signal reduction is usually found with a unilateral preference. With further progression and degeneration in later disease stages signal reduction appears bilaterally (Fig. 1a). According to a study of 122 patients with iPD, the DaTSCAN shows different patterns in tremor-dominant versus akinetic-rigid iPD (Eggers et al., 2011). Unfortunately, the $^{123}$I-FP-CIT SPECT does not reliably distinguish iPD from atypical parkinsonian syndromes, such as MSA, PSP, CBD and a similar nigrostriatal deficit is also detected in LBD (Pirker et al., 2000; Kägi et al., 2010). Other imaging techniques focusing on the D2-receptor expression are more useful to answer this question. As mentioned earlier, autonomic denervation is an early phenomenon in iPD and $^{123}$I-MIBG scintigraphy is a mean to visualize the postganglionic, presynaptic sympathetic terminals.

![Fig. 1. a: DAT-SPECT; transversal section; 3 h after injection of 220 MBq $^{123}$I-FP-CIT (DaTSCAN®). Left: normal dopamine transporter labeling. Right: reduced putaminal dopamine transporter labeling suggestive of a nigrostriatal deficit (e.g. iPD, LBD, MSA). b: D2-receptor-SPECT; transversal section; 1,5 h after injection of 185 MBq $^{123}$I-IBZM. Left: normal D2-receptor expression with good contrast in the basal ganglia relative to cortex. Right: reduced D2-receptor expression with low contrast of basal ganglia relative to cortex (e.g.: MSA).](www.intechopen.com)
al., 2006). Due to better sensitivity and the correlation to clinical progression the DaTSCAN currently may be more suitable in the early diagnosis of iPD than $^{[123]}$I-MIBG scintigraphy. SPECT imaging also allows quantifying the postsynaptic dopamine receptor status, which can be helpful in the differentiation of iPD and atypical parkinsonian syndromes. D2 receptors can be imaged by application of $^{[123]}$I-IBZM or $^{[123]}$I-IBF and are decreased in atypical parkinsonian syndromes, such as MSA or PSP, but normal or even upregulated in early iPD (Kim et al., 2002) (Fig. 1b). Imaging techniques aiming at the visualization of cerebral blood flow, such as $^{[99mTc]}$-ECD (so-called Neurolite) or FDG, can help in the identification of corticobasal degeneration, where an asymmetrical reduction of perfusion in cortical areas can be revealed (Hossain et al., 2003) and discriminate towards PSP (Zhang et al., 2001). Non-dopaminergic functions are also accessible to PET and SPECT imaging, although these examinations are not performed routinely. For example, the $^{11}$C-WAY100635 PET can visualize reduced serotonin receptor expression in iPD, which has been suggested to play a role in iPD-associated depression, and evaluation of $^{11}$C-PK11195 binding by PET examination reflects microglial activation associated with iPD (Brooks, 2007).

### 3.1.3 Transcranial ultrasound

Transcranial ultrasound has meanwhile become a standard exam for the initial bedside diagnostics in suspected iPD. Since the first description of hyperechogenicity in the substantia nigra in iPD patients (Becker et al., 1995) a large number of studies confirmed these findings demonstrating that these alterations occur in more than two thirds of all iPD patients and that substantia nigra hyperechogenicity is detectable in a very early stage of disease (Fig. 2). Although the histopathological correlate of this alteration is still a matter of debate, there is evidence to suggest that increased iron deposition and/or microglial activation is responsible for this phenomenon. As in each ultrasound examination, the quantification and quality of the readout depends highly on the skill of the examiner, but as recent studies have shown, reproducibility in experienced sonographers is high (van de Loo et al., 2010). Because 10% of healthy controls also show hyperechogenicity in the substantia nigra (Berg et al., 2001), the ultrasound may not serve as a screening method for a general population, but rather as a supporting exam in suspected iPD.

![Fig. 2. Transcranial B-Mode sonography of the midbrain (purple dotted line). Controls show little to no hyperechogenicity (white dotted line) in the substantia nigra (a) as compared to markedly increased hyperechogenicity in iPD patients (b).](www.intechopen.com)
3.2 Laboratory analysis
Up to now, no laboratory test is available for the diagnosis of iPD and no single marker has been identified so far (see section 5). There is no routine workup, but assessment of serum copper and ceruloplasmin as well as urine copper may be indicated especially in patients with young onset PD, if Wilson’s disease is suspected.

3.3 Other technical exams
3.3.1 Olfactory testing
Olfactory testing is an inexpensive, but useful supplementary exam and should be performed in each patient presenting with suspected iPD. Commercial kits are available, where different odorants, including trigeminal irritants and controls, are presented to the patient (e.g. Sniffin’ Sticks®, (Wolfensberger and Schnieper, 1999). Most patients (90 %) with iPD show olfactory dysfunction early in the disease course (Katzenschlager and Lees, 2004). There are therefore reasons to suggest olfactory testing as an early clinical biomarker for iPD (Morley and Duda, 2010). Olfaction can also be impaired in patients with MSA, but it seems to be mostly unaffected in PSP or CBD (Wennig et al., 1995; Müller et al., 2002). Therefore, olfactory testing can be a useful additional tool in the differentiation between iPD and atypical parkinsonian syndromes.

3.3.2 Genetic testing
If a family history of Parkinson’s disease exists or if disease manifestation occurs at a young age, patients may benefit from genetic counselling. Up to now, at least 6 PD susceptibility loci have been identified and at least 11 other genes are known to cause genetic Parkinson’s disease (reviewed in (Shulman et al., 2010). A recently published study identified individuals with an age of onset of 30 years or younger (50 years or younger in patients with Jewish or Hispanic ancestry) or those with a history of Parkinson’s disease in a first-degree relative as most likely to bear a mutation in a iPD-associated gene (Alcalay et al., 2010). These patients may undergo genetic testing after thorough information about possible consequences of the test results for family members, familial planning and prognostic considerations.

3.3.3 Dopaminergic response test
The histopathologically prominent nigrostriatal degeneration and the consecutive depletion of dopamine in the striatum can be identified as the pathoanatomical and biochemical correlate of the motor symptoms in iPD, most importantly of the bradykinetic symptoms. Thus, it is not surprising that dopamine replacement therapy initially results in transient, but marked amelioration of these symptoms, an effect which patients often experience as the “honeymoon-phase” due to the dramatic symptom reduction. Responsiveness to dopaminomimetic therapy is an important supportive factor for the confirmation of the diagnosis of idiopathic Parkinson’s disease and a lacking improvement of motor symptoms suggests the presence of an atypical parkinsonian syndrome, such as PSP, MSA or CBD. Clinical testing for dopaminergic response can be performed with levodopa (e.g. 200/50 mg levodopa/dopadecarboxylase inhibitor) by oral application or with apomorphine, a dopaminergic drug requiring subcutaneous administration. The test is usually considered positive, if the patient improves by at least 30 % in the UPDRS – a number which may be too ambitious in patients presenting only with mild symptoms (Reichmann, 2010). It has to be considered though, that even atypical parkinsonian syndromes may show an initial response to L-DOPA therapy, which usually is transient and less pronounced than in
iPD (Srulijes et al., 2011). Also, tremor is the symptom, which is most resistant to dopaminergic therapy and therefore may result only in an insufficient response.

4. Differential diagnosis

In the following part of this chapter, a number of clinically relevant differential diagnoses are discussed. The main clinical differences are presented along with the appropriate diagnostic tools for the discrimination against iPD.

4.1 Progressive supranuclear palsy (PSP)

As one of the most frequent atypical parkinsonian syndroms, PSP belongs to the group of so-called tauopathies, disorders which are characterized by pathological processing of the tau protein. Compared to iPD, PSP is still quite rare (1-6/100,000 inhabitants) (Schrag et al., 1999; Nath et al., 2001). Clinically, at least two distinct variants can be differentiated: PSP-parkinsonism (PSP-P) and the Richardson’s syndrome (RS). While PSP-P initially may present with typical iPD-features, such as tremor, bradykinesia, rigidity and even a temporary response to dopaminergic medication, other symptoms, such as the supranuclear vertical gaze palsy, postural instability and cognitive decline take center place in the later course of the disease (Litvan et al., 1996). In RS (the original syndrome described by Richardson in 1963) these additional symptoms are present in the very beginning of the disease (Richardson et al., 1963). The protracted appearance of these additional symptoms in PSP-P may complicate the diagnosis and it’s no surprise that less than 50% of pathologically verified PSP-cases are not diagnosed correctly at their first visit (Osaki et al., 2004).

Fig. 3. Characteristic MRI findings in PSP and MSA. Thinning of cerebral peduncles (“Mickey mouse sign”) (a) and mesencephalic atrophy (“hummingbird sign”) (b) on T2-weighted images in PSP. Cerebellar and pontine atrophy (c), hyperintense putaminal rim (d) and degeneration of pontocerebellar projections (“hot cross bun sign”) (e) as observed on T2-weighted images in patients with MSA.
In clinical differentiation, the symmetrical and mostly axial presentation of bradykinesia, frequent falls and an initially pathological pull test for postural instability should direct attention towards possible PSP. A positive “applause sign” (a tendency to continue applauding after having been instructed to clap three times) may be useful in the differential diagnosis between iPD and PSP, but it has been recently recognized to be even more specific for CBD patients (Dubois et al., 2005; Wu et al., 2008). Pathological tracer distribution in the $^{[123]}$I-IBZM-SPECT may also be found in PSP (see 3.1.2). On MRI examination patients with PSP may display a mesencephalic atrophy, which can appear as so-called “penguin sign” or “hummingbird sign” in the mid-sagittal section (Oba et al., 2005). On axial T2-weighted sections, the anteroposterior diameter of the midbrain is reduced and, together with a thinning of the cerebral peduncles, may result in the so-called “mickey mouse sign” (Fig. 3a). The reduction of a-p diameter below 14 mm seems to specifically differentiate patients with PSP from iPD (Warmuth-Metz et al., 2001).

4.2 Multiple system atrophy (MSA)

As an atypical parkinsonian syndrome multiple system atrophy (MSA) has a slightly lower prevalence than PSP. Similar to iPD, MSA is an alpha-synucleinopathy, but here inclusions are found in oligodendrocytes instead of neurons (Tu et al., 1998). Because patients can present with a primarily parkinsonian or a primarily cerebellar phenotype a differentiation into MSA-P and MSA-C is clinically used. MSA-P patients can initially show typical signs of iPD, but additional signs, such as orthostatic hypotension, urinary incontinence and erectile dysfunction should be regarded as red flags for the diagnosis of MSA. Cerebellar dysfunction with ataxic gait and limb movements, dysarthria and sustained gaze-evoked nystagmus may initially lead in MSA-C patients, but may also be present or appear in the course of the disease in patients presenting with MSA-P. Some patients may also show positive corticospinal tract signs (Gilman et al., 1999). Response to dopaminergic medication can be initially positive, but the effects are mostly transient (Hughes et al., 1992).

SPECT imaging using $^{[123]}$I-IBZM may show decreased D2 receptor binding in MSA, but measurements of the striatal regional apparent diffusion coefficients (rADC) by diffusion-weighted images on MRI scans (MRI-DWI) may be even more sensitive in differentiating MSA from iPD (Seppi et al., 2004). Conventional MRI in MSA-P can show a hyperintense putaminal rim on T2-weighted images. Cerebellar and pontine atrophy as well as a cross-like hyperintensity on T2-weighted images (so-called “hot-cross-bun”-sign reflecting the degeneration of pontocerebellar projections) can also be observed in MSA-C (Fig. 3b-d)(Lee et al., 2004).

4.3 Corticobasal degeneration (CBD)

This rare tauopathy may have more common features with frontotemporal dementia (Pick’s disease) or PSP than with iPD, but an initial appearance with unilateral bradykinesia and tremor may evoke the latter differential diagnosis. Red flags for the presence of CBD are a slowly progressive unilateral apraxia together with dystonia and jerky movements mostly in the upper limb as well as a visual-tactile neglect. The so-called “alien-limb sign”, indicating the loss of voluntary control over one extremity, is present in about half of the patients. Signs of corticospinal tract degeneration, dysarthria, gait difficulties and supranuclear ophthalmoplegia can be found in the later disease course (Rinne et al., 1994). Cognitive decline with development of dementia is frequent (Grimes et al., 1999).

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4.4 Essential tremor (ET)
A positive family history, clinical responsivity to beta-blockers and small doses of alcohol suggests the presence of ET. Rest tremor is unusual in ET and the manifestation is mostly as a symmetrical, postural and kinetic tremor (Bain et al., 2000). Since tremor may be one of the first and sometimes solitary symptoms at initial presentation of iPD, differential diagnosis may be difficult. DaTSCAN analysis should usually be able to differentiate versus iPD by exclusion of a striatal dopaminergic deficit, but a clinical overlap has been suggested and it is still controversial whether at least a subgroup of ET patients may develop iPD and vice versa (Quinn et al., 2010).

4.5 Lewy-body dementia (LBD)
Histopathology suggests that LBD and iPD may indeed be very similar disorders and probably can be considered as a neuropathological spectrum of an alpha-synucleinopathy with Lewy bodies (Jellinger, 2009). As the name suggests, cognitive decline is the primary feature in LBD and – per definition – must be present before the onset of motor dysfunctions, which most frequently present as bradykinesia and rigidity. The clinical challenge is the separation from Parkinson’s disease dementia, which may occur in up to 40% of all iPD patients (see section 2.2.4). The term Parkinson’s disease dementia should only be used when dementia occurs at least 12 months after onset of motor symptoms in iPD, which however is an arbitrary cut-off. According to consensus criteria, LBD patients show also pronounced fluctuations in cognition and attention. Also, optical hallucinations can occur and patients can display a marked sensitivity to neuroleptic treatment (McKeith et al., 1996; McKeith et al., 2005).

4.6 Vascular parkinsonism
It is now widely acknowledged that white matter changes observed in arteriosclerotic disease, e.g. due to long history of arterial hypertension, may be associated with the presentation of parkinsonian-like features. However, there are no commonly-accepted diagnostic criteria,
which may be due to the heterogeneity of this disorder as well as a possible coincidence of vascular changes and iPD. Clinically, patients may present with a slowly progressive difficulty of gait, while the upper extremities usually are less affected – thus the term “lower-body parkinsonism”. Tremor is less frequent, but patients may show a multitude of additional symptoms, such as corticospinal tract signs, pseudobulbar palsy, dementia or incontinence, depending on the distribution of the microvascular alterations (systematically reviewed in Kalra et al., 2010). Rarely, symptoms occur abruptly after an ischemic incidence (Alarcón et al., 2004). Response to dopaminergic therapy usually is limited.

In contrast to iPD, the native CT scan and the MRI may be helpful in the identification of vascular lesions and a history of arteriosclerosis, hypertension and other cardiovascular risk factors may be indicative.

4.7 Normal pressure hydrocephalus (NPH)

Because of the therapeutic consequences arising from the diagnosis of NPH and its relatively high prevalence, it is of high clinical relevance to differentiate this disorder from iPD. Recent estimates of the prevalence with ~22/100,000 inhabitants are very likely understated (Brean and Eide, 2008). Cognitive decline up to dementia as well as urinary incontinence in combination with a gait disturbance build the classical triad of symptoms initially described by Hakim and Adams (Hakim and Adams, 1965). Not all patients, however, present with all three symptoms at the initial visit, which may delay diagnosis. In addition, the slow, shuffling and broad-based gait shows striking similarities to the one observed in iPD (Bugalho and Guimarães, 2007).

Enlarged ventricles can be observed on CT or MRI scans (Fig. 5) and the diagnostics should be followed by a large-volume lumbar puncture. Structured analysis of gait and cognitive function has to be performed before and after taking CSF. An improvement, which is most likely to occur in the gait analysis, favours the diagnosis of NPH and permits to identify patients, who will benefit of ventriculoperitoneal shunting (Bergsneider et al., 2005).

Fig. 5. Characteristic findings in NPH. Enlarged ventricles without pronounced global atrophy on CT scan (a), axial MRI T1-weighted (b) or sagittal T2-weighted images (c).

4.8 Drug-induced Parkinsonism

Different medications can result in a clinically apparent parkinsonism. The symptoms are usually symmetric and tremor is less frequent in contrast to iPD (reviewed in Susatia and Fernandez, 2009). Most importantly, dopamine receptor blockers (e.g. neuroleptics or antiemetics) and other dopamine-depleting drugs have to be considered (Ebadi and Srinivasan, 1995). However, valproic acid, lithium, flunarizine as well as some SSRIs have also been reported to cause extrapyramidal symptoms (Susatia and Fernandez, 2009).
The prognosis of drug-induced Parkinsonism is rather good as most patients recover after discontinuation of medication. If parkinsonian symptoms are not reversible, one should consider the presence of iPD, which has been unmasked by the anti-dopaminergic medication.

4.9 Other differential diagnoses
In addition to the above-mentioned disorders, there are a number of less frequent causes for parkinsonian syndromes. Because basically any kind of lesion to the extrapyramidal system can potentially result in a parkinsonian presentation, the list of possible etiologies cannot be complete. Some of them have been listed as exclusion criterion in the UKPDSBB clinical diagnostic criteria, for example repeated head trauma, history of encephalitis, cerebral tumour or MPTP exposure (see Table 1). Other neurodegenerative (Huntington’s disease, spinocerebellar ataxia, frontotemporal dementia), neurometabolic (Wilson’s disease, Fahr’s disease, hypoxia) or toxin-induced (occupational manganese exposure, carbon monoxide intoxication) disorders can also present with signs of parkinsonism, even though usually other symptoms are additionally present (reviewed in (Tolosa et al., 2006)).

5. Strategies to improve diagnostic security and early diagnosis
The need to establish an early and reliable diagnosis resulted in a vast ongoing research activity to identify early biomarkers for iPD. Numerous studies focussed on serum or CSF samples, because these fluids can be easily collected and are readily available for large-scale examinations. Numerous publications document the effort to analyze levels of candidate proteins as putative biomarkers, i.e. alpha-synuclein, oligomeric alpha-synuclein, tau, abeta, DJ-1 and combinations thereof, just to name a few (Tokuda et al., 2006; Borroni et al., 2008; Waragai et al., 2010; Tokuda et al., 2010). A recently published large cohort study could show reduced alpha-synuclein levels in synucleinopathies (DLB, iPD and MSA), but was not able to discriminate between these different entities (Mollenhauer et al., 2011). Levels of dopamine metabolites (Lunardi et al., 2009), transition metals (Jiménez-Jiménez et al., 1998) or neurotrophic factors (Pålhagen et al., 2010) have also been quantified, but at the moment there is no clinically helpful single biomarker or combination of biomarkers available. Novel imaging techniques mainly based on MRI algorithms could move the field forward, but an automated analysis of several parameters appears to be mandatory and has not yet reached clinical practice (Jubault et al., 2009; Vaillancourt et al., 2009; Boelmans et al., 2010; Jubault et al., 2011). Next to imaging and laboratory analysis the identification of clinical markers may be even more important, since preclinical symptoms precede the onset of motor symptoms significantly. A combined strategy taking into account a cumulative score involving premotor symptoms, such as olfactory dysfunction, sleep disorders and neuropsychiatric disorders could be a promising approach and will have to be evaluated for its prognostic value (reviewed in (Wu et al., 2011)).

6. Summary
The diagnosis of idiopathic Parkinson’s disease is mainly based on clinical criteria of motor symptoms, such as bradykinesia, tremor and rigidity. If these are met, other signs of atypical and secondary parkinsonian syndromes, for example MSA, PSP, CBD, vascular parkinsonism, NPH or LBD have to be excluded. In addition to clinical signs typical of these disorders, auxiliary exams, including olfactory testing, MRI and SPECT imaging can help to identify these entities.
Finally, the diagnosis of iPD is supported by prospective criteria, which have to be met during the course of the disease, such as levodopa response, asymmetric symptoms and disease progression.

There is no single reliable biomarker for iPD available yet and a definite diagnosis currently can be made only by histology.

### 7. References


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Parkinson's disease is diagnosed by history and physical examination and there are no laboratory investigations available to aid the diagnosis of Parkinson’s disease. Confirmation of diagnosis of Parkinson’s disease thus remains a difficulty. This book brings forth an update of most recent developments made in terms of biomarkers and various imaging techniques with potential use for diagnosing Parkinson’s disease. A detailed discussion about the differential diagnosis of Parkinson’s disease also follows as Parkinson’s disease may be difficult to differentiate from other mimicking conditions at times. As Parkinson’s disease affects many systems of human body, a multimodality treatment of this condition is necessary to improve the quality of life of patients. This book provides detailed information on the currently available variety of treatments for Parkinson’s disease including pharmacotherapy, physical therapy and surgical treatments of Parkinson’s disease. Postoperative care of patients of Parkinson’s disease has also been discussed in an organized manner in this text. Clinicians dealing with day to day problems caused by Parkinson’s disease as well as other healthcare workers can use beneficial treatment outlines provided in this book.

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