

Parkinson's disease between internal medicine and neurology

Ilona Csoti¹ · Wolfgang H. Jost² · Heinz Reichmann³

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Abstract General medical problems and complications have a major impact on the quality of life in all stages of Parkinson's disease. To introduce an effective treatment, a comprehensive analysis of the various clinical symptoms must be undertaken. One must distinguish between (1) diseases which arise independently of Parkinson's disease, and (2) diseases which are a direct or indirect consequence of Parkinson's disease. Medical comorbidity may induce additional limitations to physical strength and coping strategies, and may thus restrict the efficacy of the physical therapy which is essential for treating hypokinetic-rigid symptoms. In selecting the appropriate medication for the treatment of any additional medical symptoms, which may arise, its limitations, contraindications and interactions with dopaminergic substances have to be taken into consideration. General medical symptoms and organ manifestations may also arise as a direct consequence of the autonomic dysfunction associated with Parkinson's disease. As the disease progresses, additional non-parkinsonian symptoms can be of concern. Furthermore, the side effects of Parkinson medications may necessitate the

involvement of other medical specialists. In this review, we will discuss the various general medical aspects of Parkinson's disease.

Keywords Parkinson's disease · Internal disease · Comorbidity · Side effects · Interactions

Introduction

The typical cardinal symptoms of Parkinson's disease (PD) are akinesia, rigidity, tremor and postural instability. The long-term course of the disease becomes complicated by motor and non-motor fluctuations and failing efficacy of the medication (Storch et al. 2013). Specific assessments and comprehensive tools are available for diagnostic and therapeutic use (Chaudhuri et al. 2007; Marras and Lang 2008; Olanow et al. 2009; Rascol et al. 2011; Sprenger and Poewe 2013). The influence of additional medical problems on the disease course, however, has so far only been poorly described. The choice of an effective treatment for the individual is determined by a precise differential-diagnostic classification of the various symptoms, because these may have a direct impact on the severity of the impairment and mortality (Parashos et al. 2002; Elbaz et al. 2003).

This report will focus on three major sub-groups: (1) medical comorbidity, arising independently of the underlying disease, (2) clinical symptoms arising as a result of disease-associated autonomic denervation, and (3) side effects of the Parkinson's disease medication itself, which may necessitate the involvement of other specialists.

A limited number of review articles on comorbidity in PD have been published, but none of these were entirely devoted to this topic. Affective, cognitive and

✉ Ilona Csoti
ilona.csoti@t-online.de; ilona.csoti@parkinson.de

Wolfgang H. Jost
w.jost@parkinson-klinik.de

Heinz Reichmann
heinz.reichmann@uniklinikum-dresden.de

¹ Gertrudis-Clinic Parkinson-Center, Karl-Ferdinand-Broll-Str. 2-4, 35638 Leun, Germany

² Parkinson-Klinik Wolfach, Kreuzbergstr.12-24, 77709 Wolfach, Germany

³ Department of Neurology, University of Dresden, Fetscherstraße 74, 01307 Dresden, Germany

musculoskeletal comorbidities are statistically more likely to internal diseases. Chronic medical diseases, such as arterial hypertension or diabetes mellitus, despite their sometimes severe impact, have only a slight influence on overall morbidity (Leibson et al. 2006; Guttman et al. 2004; Gorell et al. 1994). This is surprising as many studies have been published in which the relationship between PD and individual diseases has been examined; however, these studies did not consider the sometimes detrimental effect the treatment of these additional symptoms can have on the further course of PD.

The possible side effects associated with Parkinson medication are numerous, and are described in detail in the summaries of product characteristics (SPC) issued by pharmaceutical companies for each product. Most of these side effects, however, are infrequent and rarely lead to discontinuation of the therapy. Cardiac valve pathology, subsequent to the use of ergoline dopamine agonists, is one of the serious side effects associated with the use of PD medication, and this led to very stringent limitations on the drug approval in 2007 and to the withdrawal of pergolide for human use in the USA (Zanettini et al. 2007). Realizing that a particular non-PD symptom may possibly be related to a dopaminergic or anti-glutamatergic therapy is essential for determining the correct course of treatment. Our report will discuss the most important side effects which can lead to either a change of or the cessation of medication.

The greatest cause of general medical problems in PD is PD itself, mostly due to the functional disturbances that arise from the autonomic denervation which affects nearly all the organs (Goetz et al. 1986; Senarda et al. 1997; Poewe 2008). For the present, the consequences of cardiac and gastrointestinal denervation in particular, and the reasons for involving specialists from other medical disciplines, will be addressed.

The reciprocal influence of general medical and neurological complications in PD requires a close and continuous feedback between the neurologists and the other medical specialists involved in the individual case. To date, there is a dearth of prospective studies on this topic.

Some of the medical complications seen most frequently in everyday clinical settings will now be examined in the following sections.

General medical comorbidity

Patients with PD exhibit a high rate of multi-morbidity. In various studies on comorbidity, up to 80 % of the patients had five or more concomitant diseases (Gorell et al. 1994; Leibson et al. 2006). The significance of this lies not only in the higher degree of stress for the patient, but also in the concomitant therapy of these medical diseases, as these can

seriously influence the overall treatment success or the rate of mortality (Parashos et al. 2002; Elbaz et al. 2003; Doi et al. 2011). Viewing the results of these studies, it is apparent that, for at least the first years of PD, typical medical diseases (such as diabetes mellitus) do not occur more frequently among PD patients when compared to control groups (Leibson et al. 2006). An increase in age-correlated comorbidity cannot be found until after 10–15 years with PD and is clearly related to complications and sequelae of PD (Leibson et al. 2006). Most frequent among these comorbidities are diseases of the joints and fractures (Leibson et al. 2006; Melton et al. 2006; Natalwala et al. 2009; Jones et al. 2012). In contrast, other intercurrent diseases such as pneumonia or cardiovascular disease are the principle cause of death in all mortality studies (Gorell et al. 1994; Ben-Shlomo and Marmot 1995; Pinter et al. 2014).

Diabetes mellitus

Although the data from several cohort studies revealed a high level of comorbidity between PD and diabetes mellitus, these results have not been consistent (Cereda et al. 2011). A number of retrospective case studies have shown a tendency for the co-occurrence of diabetes and PD, whilst other studies failed to corroborate this finding (Gorell et al. 1994; Leibson et al. 2006; Hu et al. 2007; Becker et al. 2008; Jones et al. 2012). Other clinical studies reported an increased risk of over 40 % for patients with diabetes to develop PD (Miyake et al. 2010; Xu et al. 2011; Sun et al. 2012). In one population-correlated cohort study with an observation period of 12 years, there was a 2.2-fold increased risk for contracting PD, and this risk was in fact raised by a further 57 % if the diabetics had been treated with sulfonylurea (Wahlqvist et al. 2012).

The development of diabetes by PD patients is correlated with increased cognitive deficits, gait disturbance and postural instability (Bohnen et al. 2014; Kotagal et al. 2013). Recent genetic research has found an association between both PD and diabetes mellitus and the SOD2*Val polymorphism (Santiago et al. 2014).

The oral antidiabetic, metformin, has proven to be effective in the therapy of diabetes mellitus, and now, because of its neuroprotective and pro-dopaminergic qualities, is attracting attention in animal models of PD and in the treatment of PD patients. (Wang et al. 2012; Potts and Lim 2012; Adeyemi et al. 2013; Patil et al. 2014; Wahlqvist et al. 2012). The potential deficiency in vitamin B12 which is linked to metformin use has been associated with the occurrence of polyneuropathy (Bell 2010). As polyneuropathy is a frequent neurological complication of diabetes mellitus, and as vitamin B12 deficiency has also been described in PD, screening for vitamin B12 deficiency

is recommended for patients with diabetes and PD (Kästenbauer et al. 2004; Madenci et al. 2012; Ceravolo et al. 2013). If diabetic nephropathy occurs as a result of diabetes mellitus, dose adjustment has to be considered when amantadine, bupropion and pramipexole are being prescribed (see <http://www.dosing.de>) (Horadam et al. 1981; Hong et al. 2008).

Dyslipidemia

The data on hypercholesterolemia and PD are inconsistent (Hu et al. 2008; Miyake et al. 2010). One recent meta-analysis failed to find an increased association between elevated serum cholesterol and PD (Gudala et al. 2013). HMG-CoA reductase inhibitors (statins) may arguably have an anti-inflammatory, immune-modulating and neuroprotective effect (Gao et al. 2012; Undela et al. 2013). In a meta-analysis, a relative reduction in risk of 29 % was found for PD, but only for the group of patients under the age of 60 (Gao et al. 2012). Nonetheless, the risk for cardiovascular complications is increased for patients with PD and hypercholesterolemia (Firoz et al. 2015).

Huang et al. prospectively examined plasma lipids and statin use in relation to PD in the Atherosclerosis Risk in Communities (ARIC) Study. Statin use and plasma lipids were assessed at baseline and at three triennial visits thereafter until 1998. Statin use may be associated with a higher PD risk, whereas higher total cholesterol may be associated with lower risk. These data are inconsistent with the hypothesis that statins are protective against PD (Huang et al. 2015).

Obesity

The relationship between obesity and PD is discussed very controversially. Dopamine is involved in the regulation of food intake. Obese persons have decreased dopamine D2 receptor availability in the striatum (Chen et al. 2004). Based on this scientific knowledge, the relationship between obesity and the risk of Parkinson's disease was several scientifically investigated. Chen et al. studied the association between obesity and the risk of PD in two large cohorts of US man and women from the "Health Professionals Follow-up Study" and the "Nurses' Health Study". The results do not support a role of overall obesity in PD pathogenesis, however, central obesity may be associated with higher PD risk among never smokers (Chen et al. 2004). Also in the Harvard Alumni Health Study, the body mass index (BMI) was unrelated to Parkinson's disease risk (Logroscino et al. 2007). Hu et al. found in a Finnish cohort that the risk of PD was twice as high in men with BMI over 30 and there was a 70 % higher risk among women (Hu et al. 2006).

Previous studies have also suggested an association between PD and obesity as comorbidity. In a cross-sectional study in the PD group 19.2 % were obese (Morales-Briceño et al. 2012). In a Mexican general population, the prevalence for overweight was 20.3 % (OR 1.45, $p < 0.0001$, CI 95 % 1.65–2.12), compared to general population (Llorens-Arenas et al. 2015).

Arterial hypertension

The role of arterial hypertension as a risk factor for the development of PD has been examined in a number of case-control and retrospective studies, showing that the risk for developing PD was rather lower for hypertensive patients than for those with normotension (Miyake et al. 2010; Qiu et al. 2011; Mazza et al. 2013). Cardiac denervation in PD complicates the therapy for arterial hypertension through some special features of blood pressure in PD patients. Reducing blood pressure with medication in a supine patient increases the risk of a symptomatic OH. To avoid this, prescribing short-acting antihypertensives can be recommended for the time between meals, for the later afternoon or in the evening (Mazza et al. 2013). Some of the antihypertensives (such as calcium antagonists and ACE inhibitors) are attributed with a neuroprotective effect towards the development of PD (Rodnitzky 1999; Ritz et al. 2010; Mazza et al. 2013; Sato et al. 2014), something which, however, could not be confirmed in individual studies or in a Cochrane analysis in 2011 (Simon et al. 2010; Rees et al. 2011a; Marras et al. 2012). The calcium antagonist isradipine is an exception (Simuni et al. 2010; Iljic et al. 2011; Kang et al. 2012; Simuni et al. 2013). A Phase II study is currently being conducted by the Parkinson Study Group into the drug safety and compatibility of isradipine in the modification of PD in early stages of the disease (Simuni et al. 2010). A retrospective case analysis of 341 PD patients has found interesting results, showing that co-medication with beta blockers was associated with a weaker risk of developing PD (42.4 versus 65.6 % without beta blockers in the concomitant medication) (Pagano et al. 2014).

In selecting the appropriate antihypertensives, active substances which, based on their pharmacological properties, can cause drug-induced parkinsonism, should be avoided. Studies on this relationship have been done for alpha-methyl dopa (Strang 1966; Vaidya et al. 1970; Rosenblum and Montgomery 1980), reserpine (Birkmayer and Hornykiewicz 1964; Lorenc-Koci et al. 1995), calcium channel blockers (flunarizine, cinnarizine, amlodipine) (Montastruc et al. 1994; Sempere et al. 1995; Teive 2002), diltiazem (Dick and Barold 1989; Graham and Stewart-Wynne 1994; Remblie et al. 2001), verapamil (Malaterre

et al. 1992; Padrell et al. 1995), captopril (Sandyk 1985) and moxonidine (Webster and Koch 1996).

Obstructive sleep apnea syndrome (OSAS)

Patients with PD can develop obstructive sleep apnea syndrome (OSAS). OSAS causes daytime sleepiness, nocturnal high blood pressure, and glucose intolerance. There is no conclusive evidence to support the association between PD and the prevalence of OSA. A meta-analysis evaluates five eligible studies including 322 cases and 6361 controls. The results suggest that there is a significant negative association between PD and the prevalence of OSA. Patients with PD generally have a reduced prevalence of OSA (Zeng et al. 2013). In cases of PD with moderate or severe OSAS, the use of continuous positive airway pressure (CPAP) is established in treatment. The patients responded to therapy and regained more daytime activity. Therefore, sleep diagnostic evaluation is recommended to rule out sleep apnea as a cause for hypersomnolence (Steffen et al. 2008).

Cardiomyopathy

Comorbidity between cardiomyopathy and PD is significantly raised compared to controls and reaches 19.4 % (Zesiewicz et al. 2004). One possible cause of this—the basic deficit of sympathetic innervation in PD—is still under discussion (Satoh et al. 1999). The postsynaptic noradrenaline uptake in sympathetic nerve endings of the heart, as measured with MIBG-SPECT (123-I-Meta-Iodobenzylguanidine), serves as a marker for this disorder of innervation (Satoh et al. 1999). Studies using nuclear imaging, however, failed to confirm an association between orthostatic dysregulation (the clinical correlate of an autonomous functional disorder) and the cardiovascular disorder, so that it is now being postulated that their development is fully independent of one another (Haensch et al. 2009; Leite et al. 2014). Studies undertaken in an animal model found only a weak effect of cardiomyopathy on the progression of PD (Xu et al. 2014). Similarly, no significant negative effect of Levodopa therapy on cardiac disease could be documented (Jenkins et al. 1972).

When diuretics are called for to treat cardiac insufficiency, a combination of amantadine and dyazide (hydrochlorothiazide, triamterene) should be avoided. Dyazide reduces the clearance of amantadine, and thus toxic plasma levels are possible (Wilson and Rajput 1983). Single case reports have described akinesia, tremor, drug-induced parkinsonism and severe gait ataxia arising from the use of the anti-arrhythmic amiodarone (Lombard et al. 1986; Werner and Olanow 1989; Dotti and Federico 1995;

Malaterre et al. 1997; Krauser et al. 2005; Ishida et al. 2010). The causative factor was attributed to amiodarone-induced dysfunction of the basal ganglia (Werner and Olanow 1989). A postmortem case report described the toxic accumulation of amiodarone in the basal ganglia (Ishida et al. 2010). The cumulative incidence of a possibly neurotoxic effect of amiodarone (tremor, gait ataxia, peripheral neuropathy, cognitive deficits) was found to be 2.8 % in a retrospective case analysis (Orr and Ahlskog 2009).

Gastritis and gastroesophageal reflux

The prevalence of gastroesophageal reflux disease (GERD) is high in PD, and reaches 65 % in patients 4 years after diagnosis (Makaroff et al. 2011; Maeda et al. 2013). Therapy is conducted with proton pump inhibitors (PPI). Single case studies have documented a dose-dependent increase in the incidence of vitamin B12 deficiency, fractures and infections with clostridia in at-risk patients, although it must be admitted that randomized controlled studies are as yet lacking (Hirschowitz et al. 2008; Rozgony et al. 2010; Heidelbaugh 2013). Usage of PPI in strict dosage is recommended and should be adhered to these patients with GERD (Abraham 2012; Leibson et al. 2006; Madenci et al. 2012).

Helicobacter pylori infection

The prevalence of helicobacter pylori (HP) infection in PD patients is high and ranges from 37 to 59 % in different publications (Rees et al. 2011b). In several case-control studies, a negative influence has been reported for HP infection of the stomach lining on the absorption of levodopa and subsequent motor behavior in patients with PD (Tan et al. 2014b). According to some authors (Pierantozzi et al. 2006; Lee et al. 2008), eradication improves the effect of the levodopa and leads to a reduction in the rate of fluctuations. A review article from the Cochrane Collaboration, however, found but few indications for an improvement in motor behavior, so that screening of PD patients for HP cannot be recommended at present (Rees et al. 2011b). As a result of untreated and chronic gastritis due to HP infection, an iron deficiency anemia can occur which disappears spontaneously after successful eradication. One study involving 22 patients, however, found no difference between eradication with and without iron substitution (DuBois and Kearney 2005). If iron substitution is considered necessary in Parkinson's patients, an interval of at least 2 h should be observed between the use of the iron preparation and levodopa/DDCI or a COMT inhibitor, as otherwise chelation can occur (Orama et al. 1997; Kaakola 2000).

Small intestinal bacterial overgrowth syndrome (SIBO)

Several studies have reported finding an increase in the prevalence of small intestinal bacterial overgrowth syndrome (SIBO) in PD (Gasbarrini et al. 2007; Gabrielli et al. 2011). A possible association of SIBO presenting with gastrointestinal symptoms and a worsening of motor behavior is being considered at present (Gasbarrini et al. 2007; Fasano et al. 2013; Tan et al. 2014a). In a study involving 33 patients and 30 controls, 54.5 % of PD patients and only 20 % of controls ($p = 0.01$) had SIBO. The affected PD patients had longer off-phases and more frequent delayed-on and no-on episodes (Fasano et al. 2013). Gastrointestinal hypomotility in PD with delayed peristalsis and a disorder in the functioning of the Valva ileocaecalis are under consideration as the possible causal factor (Gabrielli et al. 2011). Under standard study requirements, melevodopa (levodopa methyl ester) proved to be more effective than levodopa in patients with PD and SIBO due to changes in the pharmacological dynamics (Fasano et al. 2014).

Leaky gut syndrome (LGS)

Recent studies suggest that leaky gut syndrome, in association with an abnormally heightened intestinal permeability (gut leakiness) for enterobacteria and exogenic toxins from the intestinal lumen, is more frequent in PD. In view of the studies by Braak et al. (2003), the relationship between the subsequent changes in the intestine and the pathophysiology of PD has attracted substantially more attention (Forsyth et al. 2011; Scheperjans et al. 2014). LGS is presently being investigated extensively in numerous study projects [Increased Gut Permeability to Lipopolysaccharides (LPS) in Parkinson's Disease, NCT01155492, Quantitative Analysis of Gut-derived Neuropeptides in Cerebrospinal Fluid (CSF) of Patients With Parkinson's Disease and Healthy Controls, NCT01792193, etc.].

Clinical disorders arising as side effects of Parkinson's disease medication

Fibrosis and fibrotic cardiac valve damage

As early as the early 1990s, individual case reports described fibrotic changes in various organs such as pleural, pericardial and retroperitoneal fibroses in patients receiving the ergoline dopamine agonists bromocriptine, pergolide and cabergoline (Jiménez-Jiménez et al. 1995; Lund et al. 1999; Shaunak et al. 1999; Mondal and Suri

2000; Bilici et al. 2004; Apostolakis et al. 2009; Elenkova et al. 2012). In addition, since 2007, numerous observational studies have shown a relationship between the ergoline dopamine agonists pergolide and cabergoline and the occurrence of fibrotic cardiac valve damage (Antonini and Poewe 2007; Zanettini et al. 2007; Schade et al. 2007; Steiger et al. 2009). Pathophysiologically, it has been proposed that activation of the 5-hydroxytryptamine 2B receptors (5HT2B) located on the cardiac valves stimulates the growth of fibroblasts in the endocardium (Setola et al. 2003; Horowski et al. 2004). This hypothesis was confirmed in a large cohort study involving 11,417 participants. An increased incidence of fibrosis (dose dependent, over 3 mg/day) was found with pergolide (sevenfold increase) and cabergoline (fivefold increase), and both substances had a strong 5-HT2B affinity. No association could be found for ropinirole, pramipexole or rotigotine (Andersohn and Garbe 2009). According to a publication of the FDA, pergolide was then withdrawn from the market by the manufacturers (FDA 2007) while drug approval for pergolide and cabergoline was maintained in Europe and Japan but subject to the following restrictions: both dopamine agonists are considered as drugs of second choice and the maximum daily dose for both preparations is set at 3 mg. If therapy should call for one of these medications, close monitoring of echocardiographical and medical parameters is mandatory. A prior fibrotic condition or cardiac valve stenosis is a contraindication (EMA 2008).

Cardiac insufficiency

In 2012, the FDA announced for the first time that there was a possible association between pramipexole and the risk of cardiac insufficiency. Such indications had arisen in an evaluation of the side effects documented in the pramipexole approval studies from 2010 (FDA 2012). An epidemiological study performed by the manufacturer revealed an increased risk of cardiac insufficiency for pramipexole (RR 1.86) and for cabergoline (RR 2.07) (Renoux et al. 2012). In a second large cohort study, utilizing the results obtained from the United Kingdom General Practice Research Database (GPDR), the use of pramipexole was associated with a greater risk for cardiac insufficiency (odds ratio 1.61). This increase in risk was especially apparent in the first 3 months of treatment and in patients aged 80 years or over (Mokhles et al. 2012). A meta-analysis in 2014 confirmed this increased risk for pramipexole and cabergoline (Perez-Lloret et al. 2014). To date, there have been no therapy limitations or health warnings for pramipexole due to insufficient data. Use of cabergoline has been severely limited at any rate, because of the risk of developing fibrosis. Further studies were called for by the FDA.

Single case studies have reported the occurrence of cardiac insufficiency under amantadine (Vale and Maclean 1977; Parkers et al. 1977).

Peripheral edemas

The occurrence of peripheral edemas, most notably in the ankles and the lower legs, has been associated with dopamine agonists and amantadine, with the frequency ranging between 5 and 40 %. In a retrospective analysis from the CALM-PD Study, risk factors for the occurrence of peripheral edemas under pramipexole were found for female gender and cardiac comorbidity (Biglan et al. 2007). A single case of massive lymph edema associated with pramipexole treatment, which resolved following cessation of the drug, has been reported (Zavala et al. 2012). In one long-term study on ropinirole extended release, 38.6 % of the patients developed peripheral edemas (Hauser et al. 2011). A lower degree of risk was found in studies on rotigotin (7 %) and piribedil (5 %) (Giladi et al. 2013; Castro-Caldas et al. 2006). Edemas under amantadine were associated with peripheral vasoconstriction (Pearce et al. 1974).

In individual cases, amantadine has been associated with the following diseases: Livedo reticularis, SIADH (syndrome of inappropriate antidiuretic hormone secretion), hyponatremia and cornea edemas (Pearce et al. 1974; Blanchard 1990; Fraunfelder and Meyer 1990; Lammers and Roos 1993; Gibbs et al. 2005; Alonso Navarro et al. 2009; Trenkwalder et al. 2007; Kim et al. 2013).

Arrhythmia due to long QT syndrome

Some Parkinson's medications may induce prolongation of the QT interval and as a result increase the risk of arrhythmia of the Torsades de Pointes (TdP) type. For this reason, very close supervision is called for when administering budipine (Scholz et al. 2003). When two drugs with a potential for QT prolongation are administered in combination, the risk is increased by 70 % and for this very reason is contraindicated (Heist and Ruskin 2005). Even amantadine can lead to a QT prolongation (Manini et al. 2007). Drugs with this risk for QT prolongation when frequently administered in Parkinson's patients also include apomorphine, domperidone, citalopram and escitalopram. For a review of other drugs, see <http://torsades.org/medical-pros/drug-lists/drug-lists.htm>.

Diarrhea

Diarrhea is a frequent or very frequent non-dopaminergic side effect when patients are treated with COMT inhibitors (Parashos et al. 2004; Kaakkola 2010), persisting even after

patients are taken off the drug. Case reports have described the occurrence of colitis under entacapone and Stalevo® (levodopa/carbidopa/entacapone) (Maroy 2008; Lim et al. 2008). Pathological liver test results are a contraindication for COMT inhibitor therapy.

COMT inhibitors harbor the potential for liver toxicity, and in the case of tolcapone but not of entacapone, this constitutes a safety risk (Haasio et al. 2002). Following the market authorization for tolcapone in 1997, three patients died from acute liver failure, which led to the withdrawal of the drug from the European market. However, further safety evaluations led to its re-approval in 2004 (Borges 2003; Brooks 2004). Tolcapone is now considered as a COMT inhibitor of second choice in treating advanced Parkinson's disease when fluctuations are present, but nonetheless regular liver enzyme monitoring is mandated.

In rare cases even the dopa decarboxylase inhibitor benserazide (contained in levodopa/benserazide formulations) can cause diarrhea (Csoti and Fornadi 2011). Changing to levodopa/carbidopa is in most cases beneficial. The risk of diarrhea is especially apparent with single doses of benserazide of over 25 mg (as in Madopar® 250 mg). Because tolcapone, due to drug interactions, can in turn raise the benserazide levels, a combination of 200/50 mg levodopa/benserazide formulations with tolcapone should be avoided (summary of product characteristics for Tasmar 100 mg 2013).

Pathological glucose tolerance and insulin resistance under L-Dopa

Dopamine influences insulin secretion. There are descriptions in the literature of a tonic inhibition of glucose-controlled insulin secretion from the β -cells of the pancreas (Ustione et al. 2013). Sirtori et al. (1972) investigated the metabolic effect of Levodopa in 24 patients and found pathological glucose tolerance after a treatment time of 1 year and an increase in serum cholesterol of approximately 10 %. Insulin resistance has also been described as being significantly higher among Parkinson's patients with dementia (Bosco et al. 2012).

Symptoms of autonomic dysfunction

Cardiovascular autonomic disorders

Syncope in orthostatic hypotension

The most common autonomic disorder within the cardiovascular system in PD is orthostatic hypotension (OH), which in the literature is reported to affect 30–60 % of patients (Bellon et al. 1996; Senarda et al. 1997). The

assumption that this disorder does not appear until the advanced stages of PD has been disproven in more recent studies (Jost and Augustus 2015). These patients typically have a sudden drop in blood pressure below the critical limit for cerebral autoregulation after a change of position, postprandially or in the recovery phase after physical strain (Jost 1995; Loew et al. 1995; Mehagnoul-Schipper et al. 2001; Ejaz et al. 2006; Ziemssen et al. 2006). Assumed causal factors include: (1) cardiac noradrenergic denervation as demonstrated in MIBG-SPECT (meta-iodobenzylguanidine), (2) extra-cardiac noradrenergic dysfunction and (3) a disturbance of the cardiovagal and sympathetic reflex (Kaufmann and Goldstein 2013; Rahman and Goldstein 2014). In addition to cardiac denervation, OH can be increased by dehydration or medication (Jacob et al. 1997). OH as a side effect of Parkinson's disease medication has been particularly described in association with dopamine agonists and selegiline, but is also possible, according to the summary of medicinal product characteristics (SMPC), with L-Dopa, COMT inhibitors and amantadine (Sachs et al. 1985; Mesec et al. 1993; Kujawa et al. 2000; Pursiainen et al. 2007). If additional medication is required because of non-motor symptoms of the disease or concurrent diseases, a worsening of OH is possible with antihypertensives/diuretics, atypical neuroleptics (clozapine, quetiapine), alpha-receptor blockers for treatment of benign prostatic hyperplasia, antidepressants (in particular tricyclic antidepressants) and opioids (SMPC). Clinical symptoms include dizziness, drowsiness, nausea, and presyncopal or syncopal events. Typically, a painful feeling of pressure in the occipital region or the area of the neck-shoulder, the so-called "coat hanger sign" is described (Bleasdale-Barr and Mathias 1998). Therapy should initially consist of modifying both the Parkinson's and other medication and increasing liquid intake (Young and Mathias 2004; Connolly and Lang 2014). If other medications are being considered, favorable results have been obtained for domperidone, fludrocortisone, midodrine, droxidopa, pyridostigmine and fipamezole (Seppi et al. 2011; Perez-Lloret et al. 2014; Biaggioni 2014; Isaacson and Skettini 2014).

Nocturnal high blood pressure (non-dipping)

In addition to OH, 50–90 % of Parkinson's patients have an increase in blood pressure when in a supine position and, as a consequence, at night (Schmidt et al. 2009; Sommer et al. 2011; Oh et al. 2013). The occurrence of this autonomous circulatory dysregulation is not necessarily associated with OH. Such a disturbed circadian blood pressure regulation is called non-dipping and can be so pronounced that nocturnal antihypertensive medication becomes necessary (Sommer et al. 2011). In order not to

aggravate the early morning OH after rising, antihypertensives should be selected with short duration of action (Mazza et al. 2013). If the increase in nocturnal blood pressure is not recognized and treated, this becomes a major risk factor for developing left ventricular hypertrophy and an associated increased risk for cerebrovascular events (Koroboki et al. 2015).

Changes in heart rate frequency

Heart rate variability (HRV, previously termed respiratory sinus arrhythmia) designates physiological variations in heart beat intervals which range within the frequency of respiration. HRV is considered a parameter of autonomous cardiac innervation and is frequently attenuated in Parkinson's patients (Malik 1996; Haapaniemi et al. 2001). This in turn is associated with a higher rate of cardiovascular morbidity and mortality, and not only in cases of diabetes mellitus, but also in PD (Feil et al. 1994; Löllgen 1999; Chen et al. 2011). The studies published to date have failed to find a correlation between an attenuated HRV and the severity of PD, so that attenuated HRV is classified with the early autonomous disorders in PD (Harnod et al. 2014; Haensch et al. 2009; Maetzler et al. 2014).

Autonomic nervous system disorders in the gastrointestinal tract

Autonomous disorders can occur in the whole of the gastrointestinal tract. The resultant clinical symptoms vary though because of overlap with primary motor symptoms such as akinesia and rigidity (Pfeiffer 2011). The concurrent gastrointestinal diseases that result from these autonomous disorders lead to a highly significant reduction in compliance in taking the Parkinson's disease medication regularly and also to a significant degree of malnutrition with its own particularly impact (Richy et al. 2013; Sheard et al. 2013). Thus, an inverse correlation was found between PD and vitamin D deficiency, while an association with the disease-caused gastrointestinal dysfunction could not be excluded (Wang et al. 2014).

Pathological alpha-synuclein aggregates in the enteric gastrointestinal tract, the dorsal vagus nucleus and brain stem have been identified as causal factors for the occurrence of this autonomous dysfunction (Cersósimo and Benarroch 2012).

Hypersalivation/sialorrhea

A recent prevalence study involving 518 Parkinson patients reported a 52.7 % incidence of hypersalivation (Ou et al. 2014). The cause for such hypersalivation is a reduction in swallowing frequency in combination with dysphagia (Kalf

et al. 2009; Srivianitchapoom et al. 2014), while saliva production itself is in fact reduced (Cersósimo et al. 2009). Use of anticholinergic medication for treating hypersalivation is limited by the high potential for side effects (Katzenschlager et al. 2003). Positive study results are available for botulinum toxin and glycopyrrolate (Evidence Level A) (Seppi et al. 2011; Gómez-Caravaca et al. 2014, Jost 2015). The topical substances ipratropiumbromide, scopolamine and tropicamide as well as oral clonidine are classified as probably effective (evidence level B), but all these preparations have side effects. The use of radiotherapy on the salivary glands is presently being examined (Lakraj and Moghimi 2013; Gómez-Caravaca et al. 2014).

It is difficult to treat dysphagia and in advanced stages of PD it is often coupled with the risk of aspiration and aspiration pneumonia (Troche et al. 2014). Disturbed oropharyngeal phase of swallowing and a pharyngeal and esophageal dysfunction (already present in early phases of PD) with delayed or inverse bolus transport, stasis or tertiary contractions have all been identified as causes of aspiration (Leopold and Kagel 1997; Sung et al. 2010). PD is therefore classified as a risk factor for developing secondary gastroesophageal reflux disease (GERD). It can manifest as erosive reflux disease, erosive esophagitis, Barrett esophagus and extra-esophageal (Koop et al. 2005), which was confirmed by an epidemiological study on the prevalence of gastrointestinal diseases in PD (Makaroff et al. 2011).

Gastroparesis

As described above, delayed gastric emptying has a multifactorial genesis (Marrinan et al. 2014), and manifests in symptoms such as abdominal fullness, nausea, acid indigestion, lack of appetite and even vomiting (Edwards et al. 1993) and leads also to a reduction in L-dopa absorption. Closely associated with these symptoms is a delayed or no effect of onset of the dopaminergic agents with a concomitant deterioration in motor symptoms (Del Tredici and Jost 2012). Domperidone has, until now, been regarded as the gold standard for treating gastrointestinal symptoms in PD, but because of its possible cardiotoxicity (long QT syndrome) there are concerns about its safety (Lertxundi et al. 2013). According to the recommendations of the EMA, domperidone should be used in the lowest possible dosage for as short a duration as possible and the maximum duration of treatment should usually not exceed 1 week (EMA 2014). Recent studies examining the role of ghrelin in treating delayed gastric emptying and its possible neuroprotective effect in PD are of interesting regarding this topic (Karasawa et al. 2014; Bayliss and Andrews 2013). Several additional studies are currently evaluating the efficacy of a minimally invasive, laparoscopically

implanted neurostimulator for treating gastroparesis (Ross et al. 2014). When gastroparesis induces a significant limitation on the clinical effectiveness of orally administered Parkinson medication, transdermal, subcutaneous or percutaneous-intestinal formulations are available (Giladi et al. 2010; Martinez-Martin et al. 2014).

Constipation

Constipation, a dysfunction of the colon, is among the most frequent autonomic disorders described in PD and interestingly, may precede motor symptoms by a good many years (Martignoni et al. 1995; Rossi et al. 2014). In addition, an observational study found that constipation increased the risk of contracting PD by a factor of 4.5 (Abbott et al. 2001). Defecographic studies have shown a prolonged colon transit time, a reduction in rectal phasic contractions, abdominal muscle weakness and evidence of paradoxical sphincter contraction during defecation (Sakakibara et al. 2003). In addition to the basic autonomic disorder, obstipation can be worsened by exogenous factors such as lack of movement, dehydration, poor dietary choices, or anticholinergic medications (Rossi et al. 2014). Case studies have also documented the following complications of constipation: megacolon, pseudo-obstructions or even volvulus, ileus or intestinal perforation (Kupsky et al. 1987; Rosenthal and Marshall 1987; Marinella 1997; Tateno et al. 2011a).

A significant positive effect was found for L-dopa on disorders of anorectal function, with a resultant improvement in constipation (Tateno et al. 2011b). Macrogol (polyethylene glycol), lubiprostone and serotonin agonists have also been shown to be efficacious in the treatment of constipation in PD (Zangaglia et al. 2007; Del Tredici and Jost 2012; Nurko and Saps 2014; Rossi et al. 2014). The use of probiotics by PD patients was shown to be associated with an improvement in stool consistency and the frequency of bowel evacuation (Cassani et al. 2011). In addition to non-pharmacological treatment (for example pelvic floor exercise, biofeedback), L-Dopa, apomorphine injections and botulinum toxin-A injections into the puborectalis muscle have proven useful in rare cases of rectal dysfunction due to abdominopelvic dyssynergy (Rossi et al. 2014). Dietary measures and the cessation of anticholinergic drugs should precede any additional drug or invasive therapy.

Summary

Parkinson's disease is a chronic and progressive neurodegenerative disorder in which the motor disturbances and emotional and cognitive deficits are the most prominent

features. Present day treatments such as combined L-dopa/dopamine agonist therapy administered either orally, subcutaneously or transdermally, and neurosurgical interventions which target these symptoms have proven to be of some success, yet these symptoms are not the only symptoms of concern. In the long-term course of the disease, therapy becomes increasingly complicated, in particular because of symptoms which arise as a result of the non-dopaminergic side effects of Parkinson's medication, concomitant diseases acquired with aging and the large number of additional autonomic disorders.

The gastrointestinal symptoms associated with Parkinson's disease are a good example of the further medical complications which patients may develop. Helicobacter pylori infections in the stomach, abnormal bacterial colonization of the small intestine and constipation are not only under consideration as potential risk factors for the development of PD, but also may arise as a consequence of PD, due to its detrimental consequences on gastrointestinal motility. Malabsorption may occur subsequent to bacterial contamination of the small intestine, leading to deficiency of vitamin B12, for example. Such deficiencies are more frequent in patients with PD and lead to a deterioration in the rate of morbidity and mortality (Gasbarrini et al. 2007; Orr and Ahlskog 2009; Tan et al. 2014a, b).

Treatment safety for our patients depends vitally on the careful observation of undesired side effects of medication, and precisely monitoring, systematically evaluating and designing therapy recommendations. This basic principle has of course been implemented in the recent past in drug therapy for Parkinson's and has consequently led to restrictions on approval and market withdrawals, and also to re-approvals with improved compulsory requirements. Only with further randomized and controlled studies involving a sufficiently high number of participants, will severe side effects be reduced or completely avoided.

The large extent of autonomic disorders in the entire sympathetic and parasympathetic nervous systems and the concomitant associated large variety of clinical symptoms necessitate a detailed knowledge of this neurological disease with its associated additional medical consequences. Adequate long-term therapy is only possible through the close cooperation of the different specialists involved.

Compliance with ethical standards

Conflict of interest Ilona Csoti has received honoraria for presentations/lectures or advisory boards from Boehringer Ingelheim, Desitin, Orion, Lundbeck, Licher MT, MEDA Pharma, Novartis, TEVA, UCB Pharma, and Zambon. Wolfgang Jost was acting on Advisory Boards, gave lectures and received research grants from Abbvie, Desitin, Medtronic, TEVA, UCB Pharma, and Zambon. Professor Reichmann was acting on Advisory Boards, gave lectures and received research grants from Abbott, Abbvie, Bayer Health Care, Boehringer/Ingelheim, Britannia, Cephalon, Desitin, GSK,

Lundbeck, Medtronic, Merck-Serono, Novartis, Orion, Pfizer, TEVA, UCB Pharma, Valeant, and Zambon.

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