J Neural Transm (2016) 123:65–71
DOI 10.1007/s00702-015-1481-6

Laboratory assessments in the course of Parkinson's disease: a clinician's perspective

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Received: 10 June 2015 / Accepted: 2 November 2015 / Published online: 14 November 2015

Abstract Physicians, caregivers and patients themselves must be alert to the onset of and changes in motor and non-motor features during the course of Parkinson's disease (PD). Parallel laboratory routine assessments are necessary because of the evolving impairment of the general health status of the individual. A number of potential biomarkers for the diagnosis of PD are currently under investigation, with diagnosis early in the disease course a particular goal, even before the onset of motor symptoms. The aim of this guideline article is to provide user-friendly, clinical evidence-based recommendations for using laboratory pathological testing for the diagnosis and differential diagnosis of PD, for assessing its time course, and managing complications of long-term dopaminergic therapy and the disabling motor features that develop in the later stages of the disease.

Keywords Parkinson's disease · Diagnosis · Levodopa · Laboratory · Surveillance

Introduction

Rigidity, akinesia and resting tremor are regarded as the major motor symptoms of Parkinson's disease (PD); later in the course of the disorder, they are joined by disturbances of balance that increase the risk of falls. These classic motor symptoms are accompanied by a wide array of initially unspecific non-motor signs (Przuntek et al. 2004; Chaudhuri and Schapira 2009). The entire range of PD symptoms is largely the result of deficient biogenic amine neurotransmission in certain brain regions. The clinical presentation of symptoms and their progression

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differs between individuals. Nevertheless, the chronic degeneration of the brain areas implicated in PD exhibits a continuous spreading that conforms to some extent to stereotypical neuroanatomical rules (Przuntek et al. 2004).

The nigrostriatal dopamine deficit is primarily responsible for the onset of motor impairment in PD. Compensation of this deficiency with dopaminergic drugs principally ameliorates akinesia and rigidity, and to a lesser extent tremor, whereas disturbances of postural reflexes do not respond to drug treatment. The resulting improvement in motor performance also reduces the severity of non-motor traits of PD to a considerable extent. The non-motor features may also respond to psychopharmacological therapy, such as the treatment of depression with antidepressants.

On the other hand, increased severity of non-motor symptoms may precede deterioration of motor performance after the PD patient has suffered a decline in their general health; for instance, after an infection or worsening of concomitant disorders. Physicians, caregivers and patients themselves must, therefore, continuously be alert to any changes in motor and non-motor performance. In these cases, routine laboratory investigations should be undertaken frequently and as soon as deterioration of general health is noted. The aim of this guideline article is to provide user-friendly, clinical evidence-based recommendations for using laboratory diagnostics in the diagnosis and differential diagnosis of PD, in the evaluation of its time course, and for managing the complications of long-term dopaminergic therapy as well as the disabling features that occur in later stages of the disease.

Methods

These recommendations were produced by a workshop consortium of German clinical and biochemical experts in the diagnosis and treatment of PD. Their task was to discuss and evaluate laboratory diagnostics based on a systematic literature research. An investigation was defined as "necessary" in cases where it is clinically obligatory. "Optional" investigations complement the necessary analyses. A test was classified as "on justified suspicion" where it should only be undertaken if there was some suspicion, based on the patient's individual history or neurological status that it might be positive. Assessments "of scientific value" are of purely theoretical interest. This classification schema was the result of the subjective consideration of the expert group of the various procedures for laboratory investigations in blood, cerebrospinal fluid, urine, saliva, and hair in terms of their costs, difficulty, clinical relevance and value in the routine clinical management of PD patients. All experts emphasized that the results of this compilation represented only a recommendation, and should not have the character of an official guideline.

Controversial issues

There was debate within the expert group about how often laboratory investigations should be undertaken on a routine basis at various stages in the course of the disease. All agreed that no well-defined, clinical hallmarks for disease progression exist beyond the initial diagnosis of PD. The expression and severity of motor symptoms also depend on the quality of the dopamine substitution therapy. Accordingly, clinical scores using rating scales, such as the Unified Parkinson's Disease Rating Scale, may vary during the course of PD.

There was also considerable debate regarding the value of the Braak model staging of PD. It was ultimately rejected, as the model depends on pathological findings and misses clear, reliable and well defined hallmarks recognized by clinicians when treating PD patients in daily practice (Braak et al. 2003; Burke et al. 2008). The onset of specific non-motor symptoms may recurrently occur throughout the entire disease process, and may, to a certain extent, also be a consequence of the employed drug therapy.

As a result of all these considerations, it was finally agreed to restrict attention to investigations to be undertaken during diagnosis and at the onset of non-motor symptoms.

Diagnostic process

The differential diagnosis of PD includes taking into account the individual history of the patient, and the course and severity of motor and non-motor symptoms. Initially, certain non-motor features,—such as apathy, slowness of cognition, depression, impairment of activity, one-sided pain syndromes—, precede the initially transitory, somewhat vague onset of motor disturbances (Przuntek et al. 2004; Martinez-Horta et al. 2013). At this stage, it is assumed that neuronal dysfunction or even death involves approximately 70 % of nigrostriatal dopamine-synthesizing neurons. Investigations are underway that seek to diagnose patients earlier with, for example, functional imagings, parenchymal sonography, specific questionnaires and further more-or-less non-specific instrumental tools for examining individuals with a certain awareness of PD and a genetically determined risk factor or PD (Berg et al. 2013). Genetic polymorphisms or parameters that can be assessed, for instance, in saliva, have been identified, but they await confirmation of their validity in the clinical setting (Devic et al. 2011; Al-Nimer et al. 2014; Stewart et al. 2014).

Table 1 Laboratory pathology for the differential diagnosis of Parkinson's disease

Parameter	Specimen	Differential diagnosis	Recommendation for use
T3, T4, TSH	Blood	Thyroid function	Essential
Bound copper	Blood	Wilson disease	On justified suspicion
Coeruloplasmin	Blood	Wilson disease	On justified suspicion
Free copper	Blood	Wilson disease	On justified suspicion
Heavy metals	Blood	Intoxication	On justified suspicion
Lead	Blood	Intoxication	On justified suspicion
Lithium	Blood	Intoxication	On justified suspicion
Manganese	Blood	Intoxication	On justified suspicion
Mercury	Blood	Intoxication	On justified suspicion
Valproic acid	Blood	Drug-induced parkinsonism	On justified suspicion
Zinc	Blood	Intoxication	On justified suspicion
Thallium	Hair	Intoxication	On justified suspicion
Copper (24 h)	Urine	Wilson disease	On justified suspicion
PARK 1–18 etc.	Blood	Genetic predisposition to parkinsonism	Scientific value (genetic)
α-Synuclein	Saliva	Genetic predisposition to parkinsonism	Scientific value (genetic)
Ferritin	Blood	Intoxication	Optional (in cases of fatigue)
ANA	Blood	Rheumatoid disorders	Optional (in cases of pain syndrome)
Anti-CCP	Blood	Rheumatoid disorders	Optional (in cases of pain syndrome)
ENA	Blood	Rheumatoid disorders	Optional (in cases of pain syndrome)
Rheumatoid factors	Blood	Rheumatoid disorders	Optional (in cases of pain syndrome)

An easy to assess, reliable screening biomarker for PD is currently not available (Gerlach et al. 2012). The diagnosis of PD is generally made after clinical examination of the patient by a movement disorders specialist. However, mild early, non-motor symptoms, particularly pain syndromes, may be underestimated by the patients and their caregivers, and can be misinterpreted by general practitioners, so that diagnosis of PD is made relatively late in the course of the disorder.

Differential diagnosis is essential. It includes exclusion of chronic or acute intoxication with copper or other heavy metals, a history of the use of parkinsonism-inducing medications (such as valproic acid), Wilson disease, rheumatoid disorders, and thyroid dysfunction. The major hematological parameters that can be assessed to exclude alternative diagnoses are summarized in Table 1. At this stage, it is also vital to screen for abnormalities of general health, such as liver or kidney dysfunction (Table 2).

Frequency of routine laboratory diagnostic procedures

These investigations should be performed once each year, and in case of "red flag" therapy-related complications, particularly the presentation of acute or chronic confusion, psychosis or delirium. The transition between these syndromes cannot well be defined, as the symptoms may vary markedly between individuals, and are heterogeneous.

Acute confusion

Sudden onset of confusion is an emergency situation. It might require morphological brain imaging for the differential diagnosis, which includes, for instance, infarctions, intracranial hemorrhage (UK)/hemorrhage (US), and CNS infections, as well as neoplastic, paraneoplastic, infectious and autoimmune meningoencephalitis. Recent changes in PD- and non-PD-related medication dosage may account also for acute confusion. A common problem is acute intoxication with dopaminergic drugs associated with dehydration or with various metabolic causes, drug interactions and side effects. The transition of this syndrome to chronic forms and to hallucinatory psychosis is fluid (Table 3).

Chronic confusion and dementia

In longer lasting states of confusion, vitamin deficiencies, intoxication, and thyroid or other hormonal dysfunctions should be considered. Screening for genetic markers of dementia, such as apolipoprotein E genotyping, is optional, as is measuring β-amyloid and tau protein concentrations in cerebrospinal fluid for confirming diagnosis of Alzheimer disease (Aarsland et al. 2014). All patients with more severe cognitive disturbances show an increased sensitivity to dopaminergic medication-induced visual delusions and hallucinations (Aarsland et al. 2014) (Table 3).

Table 2 Hematological diagnostic tests in the management of Parkinson's disease patients

Parameter	Differential diagnosis	Recommendation for use
Blood count	Inflammation	Essential
Creatinine	Inflammation	Essential
C-reactive protein	Inflammation	Essential
Electrolytes	Kidney function	Essential
Erythrocyte sedimentation rate	Inflammation	Essential
Glucose	Metabolism	Essential
Hemoglobin level	Hematosis	Essential
Leukocytes	Inflammation	Essential
Liver enzymes (GGT, GOT, GPT)	Liver function	Essential
Mean corpuscular volume (erythrocytes)	Hematosis	Essential
Platelets	Hematosis	Essential
Urea	Metabolism	Essential
Arterial blood gas analysis	Inflammation	Optional
Ammonia	Liver dysfunction	Optional
Lipase, amylase, protease	Pancreatic function	Optional

GGT γ-glutamyl transpeptidase, *GOT* glutamic–oxaloacetic transaminase, *GPT* glutamic–pyruvic transaminase

Psychosis and delirium

There is no clear distinction between the two syndromes in PD patients. The psychopathological symptoms differ between individuals, depending on the patient's personality and also, to some extent, on their environment. It is important to exclude further potential causes of this syndrome, particularly if there is no response to atypical neuroleptics (Table 4).

Depression, mania and dopamine dysregulation syndrome

Following psychosis, depressive states (in the sense of exhaustion) may appear, but depression is also frequent at different stages of PD for a number of reasons, including acceptance of the disease and increasing impairment linked with the progressive character of the symptoms. Nevertheless, further endogenous causes of depression, such as thyroid dysfunction, should be excluded. Mania and the dopamine dysregulation syndrome are frequently related to dopamine replacement therapy. The distinction from psychosis is sometimes blurred, so that laboratory investigations similar to those applied in the case of psychosis and delirium are recommended (Table 4).

However, we also recommend further regular laboratory determinations because of the typically chronic nature of PD therapy, when L-DOPA, for instance, is used.

Assessment of plasma L-DOPA may be helpful for detecting abnormalities of resorption

The oral route of L-DOPA administration and the short plasma half-life of L-DOPA result in peaks and troughs in peripheral L-DOPA levels. It is well known that gastrointestinal transport and absorption processes may also contribute to this variability. L-DOPA-containing tablets or capsules must first pass the stomach to reach the jejunal structures where most L-DOPA absorption occurs (Müller 2010). Slowed gastric emptying reduces the plasma bioavailability of L-DOPA and may delay the onset of its therapeutic effect (Nyholm et al. 2005; Müller et al. 2006; Müller 2010). A further major influence on gastrointestinal L-DOPA uptake is the intake of protein-rich food. L-DOPA is absorbed by the jejunal neural amino acid transporter; concomitant consumption of milk, meat, eggs, cheese or similar may delay the clinical effect of L-DOPA (Müller 2010).

As a result of these complex absorption mechanisms, it may be useful to determine L-DOPA and its metabolite 3-*O*-methyldopa (3-OMD) within a fixed interval (i.e., between 30 and 60 min after 100 mg L-DOPA p.o.) in instances of poor clinical response to L-DOPA. In case of abnormally low L-DOPA levels and in view of the previously mentioned key role of the gastric emptying velocity, one could repeat this investigation with soluble L-DOPA, as gastrointestinal fluid transport depends far less on the gastric emptying process (Woitalla et al. 2006; Müller 2010). Further, in cases of poor compliance and

Table 3 Recommended laboratory diagnostics for the differential diagnosis of dementia

Parameter	Specimen	Biological significance	Recommendation for use
Holotranscobalamin	Blood	Absorption, consumption	On justified suspicion (cognition, dementia, fatigue)
Methylmalonic acid	Blood	Absorption, consumption	On justified suspicion (cognition, dementia, fatigue)
Folic acid	Blood	Absorption, consumption	On justified suspicion (cognition, dementia, fatigue)
Total homocysteine	Blood	Biomarker	On justified suspicion (cognition, dementia, fatigue)
Vitamin B_6	Blood	Deficiency, consumption	On justified suspicion (cognition, dementia, fatigue)
Tau protein	Cerebrospinal fluid	Biomarker	On justified suspicion (cognition, dementia)
β-Amyloid protein	Cerebrospinal fluid	Biomarker	On justified suspicion (cognition, dementia)
Protein, cell number	Cerebrospinal fluid	Infection	On justified suspicion (acute confusion, cognition, dementia)
Apoliprotein E	Blood	Genetic predisposition for dementia	For scientific reasons (in cases presenting cognition, dementia)
MTHFR	Blood	Genetic predisposition	For scientific reasons (in cases presenting cognition, dementia, fatigue)
Intrinsic factor	Blood	Absorption	Optional (in cases presenting cognition, dementia)
Vitamin D	Blood	Absorption	Optional (in cases presenting cognition, dementia, fatigue)

Table 4 Recommended pathology investigations in case of psychosis

Parameter	Specimen	Differential diagnosis	Recommendation for use
Amphetamine	Blood	Selegiline intake	Justified suspicion
Metamphetamine	Blood	Selegiline intake	Justified suspicion
Drug screening	Urine	Intoxication	Justified suspicion
Protoporphyrin	Urine	Liver dysfunction	Justified suspicion
Digoxin level	Blood	Digoxin intake	Optional
T3, T4, TSH	Blood	Thyroid dysfunction	Optional

drug adherence, the additional assessment of the long-lasting derivative 3-OMD may be useful (Table 5). A further approach would be to measure homovanillic acid (HVA) in urine, but this surrogate marker is an unspecific derivative of several biogenic amines. Generally, urine sampling over a 24-h period is necessary for this determination, which is also more complex than blood sampling.

Assessment of vitamin levels during long-term and high-dose L-DOPA administration

L-DOPA, when administered (as is typical) in combination with a peripheral decarboxylase inhibitor (such as carbidopa), is predominantly metabolized by the enzyme catechol-*O*-methyltransferase (COMT) which catalyzes the transfer of a methyl group to L-DOPA, which is then converted to 3-*O*-OMD. This reaction is correlated with augmented synthesis of total plasma homocysteine (tHcy). An up to eightfold increase in tHcy levels above the threshold of 15 µmol/L was found during high L-DOPA/carbidopa dosing with duodenal infusion in PD patients (Manca et al. 2009; Onofrj et al. 2009; Müller et al. 2011). Vitamin B and folic acid (Müller and Kuhn 2009) are essential for the reversible enzymatic conversion of homocysteine to methionine. There are several vitamin B_{12} deficiencies that can reinforce each other, such as bacterial infection, chronic administration of histamine H_2-receptor antagonists or proton pump inhibitors, and poor nutrition. Determination of vitamin B_{12} (cobalamin) itself in plasma is not specific; a false-negative result is obtained in approximately 25 % of cases. Most serum cobalamin (80 %) is bound to transcobalamin I and III and is, therefore, not available for intracellular metabolic processes. Only the holotranscobalamin form of vitamin B_{12} is metabolically active in cells, so its assessment, in combination with methylmalonic acid determinations, may be employed to verify cobalamin deficits (Selhub 2002). Measurements of these parameters are particularly advisable during long-term chronic, high dosage L-DOPA therapy (for instance, more than 400 mg per day) or its escalation by duodenal intestinal L-DOPA/carbidopa gel (LCIG) application (Toth et al. 2010; Müller et al. 2013) (Table 5).

Table 5 Investigations for L-DOPA therapy-associated complications in blood

Parameter	Biological significance	Recommendation for use
Folic acid	Absorption, consumption	On justified suspicion (when LCIG, high oral L-DOPA dosing used)
Total homocysteine	Biomarker	On justified suspicion (when LCIG, high oral L-DOPA dosing used)
MTHFR	Genetic predisposition	For scientific reasons (when LCIG, high oral L-DOPA dosing used)
L-DOPA (levodopa)	Compliance, resorption, absorption	Optional
3-OMD	Compliance, resorption, absorption	Optional

Necessary monitoring of PD-related medications

Surveillance of hematosis, liver and kidney function is necessary because of the frequent combination of medications used in the treatment of PD (Table 1). In particular, attention should be given to rare increases in eosinophilic leukocyte numbers when using apomorphine. The COMT inhibitor tolcapone rarely causes serious hepatic reactions, with the development of severe, sometimes fatal, hepatic disease, and possibly rhabdomyolysis and a neuroleptic malignant-like syndrome. Patients with mutations in the UDP-glucuronosyltransferase 1A9 gene, which leads to defective glucuronidation activity, may be predisposed to COMT inhibitor-induced hepatotoxicity (Martignoni et al. 2005). The prescription of tolcapone currently requires strict monitoring of liver enzyme activity on a regular basis both in Europe and, to a lesser extent, in the USA. Clozapine is only approved for the treatment of psychosis in PD in Germany, but it is an excellent tremorlytic compound; when using it, however, regular blood count monitoring is required because of fatal reactions reported in the past.

Recommendations for laboratory investigations when escalating therapies in PD

Escalating therapies in PD employ the principle of continuous dopaminergic stimulation. This is the essential mode of action of LCIG and of apomorphine pump systems that, respectively, provide continuous plasma levels of L-DOPA or apomorphine (Riederer et al. 2007). This is probably also the case from the neurochemical point of view during chronic deep brain stimulation of, for instance, the nucleus accumbens, which induces striatal dopamine release (Meissner et al. 2001; Figee et al. 2014). Of these three escalation therapies, additional laboratory tests are necessary only during chronic LCIG therapy. Due to the previously mentioned observations, a continuous monitoring of the interplay between tHcy and vitamin B complex and folic acid storage and consumption during LCIG use appears advisable.

Conclusion and outlook

Laboratory investigations of parameters in body fluids are important for the differential diagnosis of PD and the monitoring of drug therapy. Continuous surveillance is recommended because of the variety of medications employed in individually balanced combinations. This is not only necessary in terms of monitoring kidney, liver, blood and immune system functions; drug level monitoring may become more critical in the future because of increasing knowledge about genetic influences on drug metabolism by various enzyme systems. The suggested L-DOPA- and 3-OMD assessments are the first step in this direction, and should be complemented by dopamine agonist level determinations and more generally available, easy to perform enzyme function tests for COMT, DOPA decarboxylase, and monoamine oxidase A and B activities.

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