Lees’ syndrome
A case series

Nilson Becker¹, Renato P. Munhoz², Hélio A.G. Teive²

ABSTRACT
We report a case series of dopamine dysregulation syndrome, previously known as hedonistic homeostatic dysregulation in patients with Parkinson’s disease on dopamine replacement therapies, now designated as Lees’ syndrome.
Key words: dopamine dysregulation syndrome, Parkinson’s disease, dopamine replacement therapy, Lees’ syndrome, impulse control disorders.

Síndrome de Lees: uma série de casos

RESUMO
Relatamos uma série de casos da síndrome de desregulação dopaminérgica, previamente conhecida como desregulação homeostática hedonística em pacientes com doença de Parkinson em uso de terapia de reposição dopaminérgica, e agora definida como síndrome de Lees.
Palavras-Chave: síndrome da desregulação dopaminérgica, doença de Parkinson, terapia de reposição dopaminérgica, síndrome de Lees, distúrbios do controle de impulsos.

Parkinson’s disease (PD) is a neurodegenerative, progressive disorder, affecting several monoaminergic systems (dopamine, noradrenaline, acetylcholine, serotonin) of the central nervous system¹. Classically, PD presents with well defined motor signs: bradykinesia, rigidity, rest tremor, and postural instability. Additionally, non-motor symptoms and signs are present in most, if not all cases, including neuro-psychiatric (e.g., depression, anhedonia, anxiety), sleep disorders (e.g., REM sleep behavior disorder, sleep fragmentation), dysautonomia (e.g., orthostatic hypotension, urinary incontinence), gastrointestinal (e.g., constipation, dysphagia), sensory (e.g., pain, hyposmia), as well as other less common symptoms (e.g., fatigue, weight loss, seborrhea)¹³. Currently, motor symptoms and signs in PD, most of them dopaminergic, can be managed with therapeutic options that include monoamine oxidase type B inhibitors (rasagiline and selegiline), dopamine agonists (e.g., pramipexole, ropinirole, piribedil, rotigotine), levodopa, catechol-O-methyl transferase inhibitors (entacapone and tolcapone), and amantadine¹².

However, several complications may occur in PD patients using levodopa, after a mean of three to five years, the so-called “honeymoon period”. These complications occur commonly in the form of motor fluctuations and dyskinesias². Later in the disease course, dopamine replacement therapy may also induce non-motor complications that include behavioral disturbances such as hypersexuality, impulse control disorders (e.g., pathological gambling, shopping, eating), aggression, hypomania, punding, craving and psychosis¹. Among these later complications of dopaminergic treatment, is the dopamine dysregulation syndrome (DDS), previously defined as homeostatic hedonistic syndrome, currently also designated as Lees’ syndrome (LS)⁴.

The objective of this study is to present a series of LS in patients with PD.

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CASES

We selected eight patients with PD, followed at the Movement Disorders Service of the Federal University of Paraná and at the Paraná Parkinson Association, who fulfilled criteria for the diagnosis of LS. Diagnosis of PD was based on the Queen Square Brain Bank criteria.

Illustrative case

A 57 year-old man, with an established diagnosis of early onset PD at the age of 43 years, started, after five years of treatment with levodopa, with motor fluctuations (wearing-off and on-off phenomena), severe peak dose dyskinesias, disabling dysarthria, hypophonias, as well as treatment refractory gait disturbances. After 10 years from diagnosis the patient underwent a right stereotactic thalamotomy performed at another service, with relative improvement on contralateral resting tremor. After another two years, He started to present re emergence of right upper limb tremor and progressive worsening of dyskinesias, also more prominent on the right. At this time he started using up to 12 tablets of levodopa/carbidopa 250/25 mg per day, compulsively and, at times, unnecessarily, according to his wife’s judgment. His drug regimen also included amantadine 100 mg bid, amitriptyline 25 mg 2 tablet bd for depressive symptoms and clonazepam 2 mg at bed time. Previously he temporarily used biperiden and pramipexole, both withdrawn due to side effects. His wife also reported episodes in which he left the house after taking two to three extra levodopa/carbidopa tablets, driving erratically at high speeds, seeking for medication obsessively at pharmacies, even after receiving medical advice to reduce its intake in several occasions. Additionally, he reported intense anxiety during medication cravings, including psychomotor agitation, restlessness, aggression towards relatives, diaphoresis, and multiple behavioral changes, including hypersexuality that led his wife to sleep in a separate room with his teenage daughter, fearing possible abuse. The patient had no co-morbidities, but his past medical history was positive for tobacco use and alcoholism. He denied illicit drug use.

General examination was unremarkable. Mini mental score examination was 20. There were dysarthria and hypophonias. Motor examination in the ON medication state showed mild rigidity on the right limbs with severe dyskinesias that spread to the neck and face.

He was admitted to the hospital, and after levodopa dosage reduction, dyskinesias improved dramatically, however, this was accompanied by significant worsening of rigidity and bradykinesia, depressive symptoms, anxiety, and continuous demand for levodopa. The later was re introduced at the dose of one tablet qid, along with

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Onset (years)</th>
<th>L-Dopa dose</th>
<th>Other drugs (mg)</th>
<th>Motor complications</th>
<th>Mood disorders</th>
<th>Behavioral disorder</th>
<th>Other symptoms/signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>57</td>
<td>43</td>
<td>2750</td>
<td>A 200</td>
<td>Fluctuations, Dyskinesias</td>
<td>Depression, Alcohol abuse, Tabagism</td>
<td>Hypersexuality, Restlessness</td>
<td>Drenching sweats</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>68</td>
<td>60</td>
<td>2000</td>
<td>B 7.5</td>
<td>Fluctuations, Dyskinesias</td>
<td>Depression, Addiction</td>
<td>Hypersexuality</td>
<td>Drenching sweats</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>58</td>
<td>43</td>
<td>2500</td>
<td>A 200</td>
<td>Fluctuations, Dyskinesias</td>
<td>Anxiety, Depression, Addiction</td>
<td>Hypersexuality</td>
<td>Drenching sweats</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>63</td>
<td>56</td>
<td>2600</td>
<td>P3, A 200</td>
<td>Fluctuations, Dyskinesias</td>
<td>Anxiety, Depression</td>
<td>Hypersexuality</td>
<td>Drenching sweats</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>41</td>
<td>29</td>
<td>1200</td>
<td>P6, A 300</td>
<td>Fluctuations, Dyskinesias</td>
<td>Anxiety</td>
<td>Paraphrenia</td>
<td>Poor hygiene</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>59</td>
<td>48</td>
<td>1000</td>
<td>P 4.5</td>
<td>Fluctuations, Dyskinesias</td>
<td>Anxiety, Depression</td>
<td>Paraphrenia, Punding</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>47</td>
<td>41</td>
<td>1800</td>
<td>A 300</td>
<td>Fluctuations, Dyskinesias</td>
<td>Anxiety</td>
<td>Restlessness</td>
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<tr>
<td>8</td>
<td>M</td>
<td>55</td>
<td>47</td>
<td>1350</td>
<td>P 5</td>
<td>Fluctuations, Dyskinesias</td>
<td>Anxiety, Depression</td>
<td>Hypersexuality</td>
<td>Drenching sweats</td>
</tr>
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</table>

LS: Lees’ syndrome; M: male; F: female; B: bromocriptine; A: amantadine; P: pramipexole.
entacapone 200 mg qd, slow release levodopa/benzer-
azine 100/25 mg at bed time, amantadine 100 mg bid.
Citalopram 30 mg qd and clozapine up to 75 mg qd were
also added. Clonazepam was kept in the original daily
dose of 2 mg at bed time. On follow up, there was par-
tial improvement of the motor and behavioral aspects
described.

An overview of the clinical and demographic data of
our series of cases of LS is shown in Table.

**DISCUSSION**

The DDS in patients with PD was described initially
in 2000, by Giovannoni et al., using the term hedonistic
homeostatic dysregulation. This designation was origi-
nally created in 1997, by Koob and Le Moal, to define
the drug abuse syndrome, characterized by the compul-
sive and uncontrolled use of drugs, due to dysfunction
of cerebral reward systems, including the dopaminergic
mesocorticolimbic pathway. Drug addiction to drugs
such as amphetamine and cocaine, is a chronic, relaps-
ning disorder, characterized basically by compulsive demand
for the specific substances, with loss of control over the
necessity to limit its use, and with the occurrence of negative emotional states (anxiety, irritability and dys-
phoria), similar to the picture of abstinence when a drug
is abruptly withdrawn. From an anatomophysiological
standpoint, the neuro-circuitry related to drug addiction
involves particularly the ventral striatum, with crucial participation of the nucleus accumbens.

From a historical perspective, there are several case
reports, starting in 1971, describing excessive intake
of levodopa accompanied by behavioral disturbances,
as well as what is described as levodopa addiction, in
patients with PD. The case report by Nausieda, for in-
stance, describes what he referred to as “Sinemet
abusers”, in 1985. Literature review shows a total of 63
publications on DDS between 2000 and 2010. The 10
most relevant, with well defined prevalence rates, di-
agnostic criteria, speculations on physiopathogenic hy-
pothesis, and analysis of comorbidities were all published
by Professor Andrew Lees’ research group from London,
UK. Accordingly, as suggested by Evans and Giovannoni
in 2008, DDS can adequately be designated as LS.

LS is a rare iatrogenic complication, observed among
PD patients with a history of long term use of dopamine
replacement therapy, characterized by the excessive use
of dopaminomimetic agents, beyond what is necessary
for adequate motor symptom control. Dopaminergic
drug abuse, is associated with the development of se-
vere dyskinesias and multiple behavioral disturbances,
including restlessness, psychomotor overactivity, aggres-
sion, hypomania, dysphoria, anhedonia, and irritability
during OFF medication periods, with compulsive de-
mand for dopaminergic drugs. Another behavioral disturbance found in these patients is punding, defined
as a complex stereotyped behavior, characterized by se-
vere fascination for repetitive manipulation of technical
equipments, by the act of collecting, examining and han-
dling common objects, as well as driving vehicles pur-
poseless or wandering. Also, Bonvin et al. recently
proposed that compulsive singing can be a another form
of punding in PD. Additionally, other behavioral distur-
bances found in LS include craving and psychosis. LS
may also encompass impulse control disorders such as
hypersexuality, pathological gambling, compulsive shop-
ning and compulsive eating.

The prevalence of LS is estimated to range from
3.4% to 4.1%, with the caveat that these numbers were
gathered from highly specialized tertiary centers. In
Brazil, references are limited to a study that assessed 100
patients with PD, where no case of LS was detected, and
a single case report by Kummer et al.

The illustrative case presented here, in a 58 year old
male with a 14 year history of early onset PD, we can
detect the typical excessive and compulsive use of le-
vodopa, beyond what is necessary to control motor
symptoms of PD, with the occurrence of severe dys-
phoria, irritability, and anxiety during OFF medication
periods, associated with drenching sweats and excessive
seeking and demand for levodopa. This case also had
a previous history of alcoholism and tobacco use, with
signs of depression as well as hypersexuality. Another
interesting aspect described here is the “self prescribed”
increase in levodopa dose, with dangerous impulsive
driving, already described by Avanzi et al. Among the
remaining cases described here, we also confirmed a sig-
ificant predominance of male patients, with hypersex-
uality, and alcohol abuse.

Among the risk factors for the development of LS
are PD onset at an early age, impulsive and sensation-
seeking personality traits, history of alcohol and drug
abuse, previous depression, as well as impulse control
disorders, punding, sleep disturbances, among others.
Schwingenschuh et al., questioned in a recent publica-
tion if PD patients engaged in artistic professional activ-
ities are at potential risk for LS. The physiopathogenic
mechanisms for LS are not yet fully understood and de-
scribed, however, the theory developed by Robinson and
Berridge has been speculated. These authors created the
incentive sensitization theory to explain LS, defining that compulsive drug use occurs due to progres-
sive neuro-adaptations formed along dopaminergic pro-
jections linked to the ventral striatum, particularly the
nucleus accumbens. This implies in persistent abnor-
malities in dopaminergic and GABAergic transmission,
with the development of sensitization and activation of
reward pathways linked to the nucleus accumbens, defined as incentive salience\textsuperscript{31}. Recent functional neuroimaging studies, such as the one published by Evans et al. in 2006, confirmed that compulsive drug use is linked to the development of sensitization of ventral striatal dopaminergic transmission\textsuperscript{32}. This sensitization induced by the use of levodopa in patients with PD, correlates with compulsive-drug seeking and punding behavior\textsuperscript{32}.

Treatment of LS has been extensively discussed. O’Sullivan et al. proposed treatment with psychotherapeutic interventions, including cognitive-behavioral therapy, surgical interventions in well selected cases (STN DBS), and pharmacological treatment with withdrawal of short acting levodopa formulations and subcutaneous apomorphine\textsuperscript{6}. For the management of impulse control disorders, withdrawal of dopamine agonists has been suggested; for the treatment of hypomania and psychosis, the use of quetiapine, clozapine or even aripiprazole. Citalopram is the drug of choice for the treatment of depression, particularly if compulsive shopping is present.

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