Article

Arq Neuropsiquiatr 2011;69(5):756-759

Lees' syndrome

A case series

Nilson Becker[1], Renato P. Munhoz[2], Hélio A.G. Teive[2]

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 system[1]. 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)[1-3]. 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 selegeline), dopamine agonists (e.g., pramipexole, ropinirole, piribedil, rotigotine), levodopa, catechol-O-methyl transferase inhibitors (entacapone and tolcapone), and amantadine[1,2].

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 dyskinesias[2]. 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 psychosis[1]. 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.

Correspondence
Hélio A.G. Teive
Serviço de Neurologia
Hospital de Clínicas - UFPR
Rua General Carneiro 181 / 4° andar
80060-900 Curitiba PR - Brasil
E-mail: hagteive@mps.com.br

Received 24 December 2010
Received in final form 27 May 2011
Accepted 3 June 2011

Movement Disorders Unit, Neurology Service, Internal Medicine Department, Hospital de Clínicas, Federal University of Paraná, Curitiba PR, Brazil: [1]Neurologist, Movement Disorders Unit; [2]Head of Neurology Service and Movement Disorders Unit.

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[5]. Diagnosis of PD was based on the Queen Square Brain Bank criteria[6].

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, hypophonia, 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 hypophonia. 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 1. Demographics and clinical data of patients with LS.

Patient	Gender	Age (years)	Onset (years)	L-Dopa dose	Other drugs (mg)	Motor complications	Mood disorders	Behavioral disorder	Other symptoms/signs
1	M	57	43	2750	A 200	Fluctuations, Dyskinesias	Depression, Alcohol abuse, Tabagism	Hypersexuality, Restlessness	Drenching sweats
2	M	68	60	2000	B 7.5	Fluctuatiuons, Dyskinesias	Depression, Addiction	Hypersexuality	Drenching sweats
3	M	58	43	2500	A 200	Fluctuations, Dyskinesias	Anxiety, Depression, Addiction	Hypersexuality	Drenching sweats
4	M	63	56	2600	P3, A 200	Fluctuations, Dyskinesias	Anxiety, Depression	Hypersexuality	Drenching sweats
5	M	41	29	1200	P6, A 300	Fluctuations, Dyskinesias	Anxiety	Paranoid ideation	Poor hygiene
6	F	59	48	1000	P 4.5	Fluctuations, Dyskinesias	Anxiety, Depression,	Paranoid ideation, Punding	–
7	M	47	41	1800	A 300	Fluctuations, Dyskinesias	Anxiety	Restlessness	–
8	M	55	47	1350	P5	Fluctuations, Dyskinesias	Anxiety, Depression	Hypersexuality	Drenching sweats

LS: Lees' syndrome; M: male; F: female; B: bromocriptine; A: amantadine; P: pramipexole.

entacapone 200 mg qd, slow release levodopa/benzerazide 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 partial 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[5]. This designation was originally created in 1997, by Koob and Le Moal, to define the drug abuse syndrome, characterized by the compulsive and uncontrolled use of drugs, due to dysfunction of cerebral reward systems, including the dopaminergic mesocorticolymbic pathway[7]. Drug addiction to drugs such as amphetamine and cocaine, is a chronic, relapsing 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 dysphoria), similar to the picture of abstinence when a drug is abruptly withdrawn[7,8]. From an anatomophysiological standpoint, the neuro-circuitry related to drug addiction involves particularly the ventral striatum, with crucial participation of the nucleus accumbens[8].

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[9-15]. The case report by Nausieda, for instance, describes what he referred to as "Sinemet abusers", in 1985[12]. Literature review shows a total of 63 publications on DDS between 2000 and 2010. The 10 most relevant, with well defined prevalence rates, diagnostic criteria, speculations on physiopathogenic hypothesis, 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[4].

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 severe dyskinesias and multiple behavioral disturbances, including restlessness, psychomotor overactivity, aggression, hypomania, dysphoria, anhedonia, and irritability during OFF medication periods, with compulsive demand for dopaminergic drugs[6,16-19]. Another behavioral disturbance found in these patients is punding, defined as a complex stereotyped behavior, characterized by severe fascination for repetitive manipulation of technical equipments, by the act of collecting, examining and handling common objects, as well as driving vehicles purposeless or wandering[16-18,20]. Also, Bonvin et al. recently proposed that compulsive singing can be a another form of punding in PD[21]. Additionally, other behavioral disturbances found in LS include craving and psychosis[16-18]. LS may also encompass impulse control disorders such as hypersexuality, pathological gambling, compulsive shopping and compulsive eating[6,16-18,22-24].

The prevalence of LS is estimated to range from 3.4%[25] to 4.1%[6], 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[26], and a single case report by Kummer et al.[27].

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 levodopa, beyond what is necessary to control motor symptoms of PD, with the occurrence of severe dysphoria, 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.[28]. Among the remaining cases described here, we also confirmed a significant predominance of male patients, with hypersexuality, 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[17,29]. Schwingenschuh et al., questioned in a recent publication if PD patients engaged in artistic professional activities are at potential risk for LS[30]. The physiopathogenic mechanisms for LS are not yet fully understood and described, however, the theory developed by Robinson and Berridge has been speculated. These authors created the incentive sensitization theory to explain LS[6,16-18,31], defining that compulsive drug use occurs due to progressive neuro-adaptations formed along dopaminergic projections linked to the ventral striatum, particularly the nucleus accumbens[31]. This implies in persistent abnormalities in dopaminergic and GABAergic transmission, with the development of sensitization and activation of

reward pathways linked to the nucleus accumbens, defined as incentive salience[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[32]. This sensitization induced by the use of levodopa in patients with PD, correlates with compulsive-drug seeking and punding behavior[32].

Treatment of LS has been extensively discussed. O'Sullivan et al. proposed treatment with psychotherapic 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[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. For the treatment of pathological gambling, opioid antagonists, lithium, valproate or carbamazepine. Amantadine has been used for the management of punding, dyskinesias and pathological gambling[6,33].

REFERENCES

1. Fox SH, Brotchie JM, Lang AE. Non-dopaminergic treatments in development for Parkinson's disease. Lancet Neurol 2008;7:927-938.
2. Lees AJ, Hardy J, Revez T. Parkinson's disease. Lancet 2009;373:2055-2066.
3. Zesiewicz T, Sullivan KL, Hauser RA. Nommotor symptoms of Parkinson's disease. Expert Rev Neurotherapeutics 2006;6:1811-1822.
4. Evans A, Giovannoni G. Dopamine dysregulation syndrome: "Lees Syndrome". In: Ockelford J, Butter J (Eds). Essays for Andrew. Dorset, UK: Remous, 2008:169-180.
5. Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatr 2000;68:423-428.
6. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51:745-752.
7. Koob GF, Le Moal M. Drug abuse: Hedonic homeostatic dysregulation. Science 1997;278:52-58.
8. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010;35:217-238.
9. Goodwin FK. Psychiatric side effects of levodopa in man. JAMA 1971; 218:1915-1920.
10. O'Brien CP, DiGiacomo JN, Fahn S, et al. Mental effects of high-dosage levodopa. Arch Gen Psychiatry 1971;24: 61-64.
11. Priebe S. Levodopa dependence: a case report. Pharmacopsychiatry 1984; 17:109-110.
12. Nausieda PA. Sinemet "abusers". Clin Neuropharmacol 1985;8:318-327.
13. Tack E, De Cuypere G, Jannes C, et al. Levodopa addiction: a case study. Acta Psychiatr Scand 1988;78:356-360.
14. Spigset O von Scheele C. Levodopa dependence and abuse in Parkinson's disease. Pharmacotherapy 1997;17:1027-1030.
15. Merims D, Galili-Mosberg R, Melamed E. Is there addiction to levodopa in patients with Parkinson's disease? Mov Disord 2000;15:1014-1016.
16. Evans AH, Lees AJ. Dopamine dysregulation syndrome in Parkinson's disease. Curr Opin Neurol 2004;17:393-398.
17. O'Sullivan SS, Evans SH, Lees AJ. Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. CNS Drugs 2009;23:157-170.
18. Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? Lancet Neurol 2003;2:595-604.
19. Evans AH, Lawrence AD, Cresswell SA, Katzenschlager R, Lees AJ. Compulsive use of dopaminergic drug therapy in Parkinson's disease: reward and anti-reward. Mov Disord 2010;25:867-876.
20. Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord 2004;19:397-405.
21. Bonvin C, Horvath J, Christe B, Landis T, Burkhard PR. Compulsive singing: another aspect of punding in Parkinson's disease. Ann Neurol 2007;62: 525-528.
22. Gallagher DA, O'Sullivan SS, Evans AH, Lees AJ, Schrag A. Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. Mov Disord 2007;22:1757-1763.
23. Ceravolo R, Frosini D, Rossi C, Bonuccelli U. Impulse control disorders in Parkinson's disease: definition, epidemiology, risk factors, neurobiology and management. Parkinsonism and Related Disorders 2009;15(Suppl): S111-S115.
24. Weintraub D. Impulse control disorders in Parkinson's disease: prevalence and possible risk factors. Parkinsonism and Related Disorders 2009; 15(Suppl 3):S110-S113.
25. Pezzela FR, Colosimo C, Vanacore N, et al. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. Mov Disord 2005;20:77-81.
26. Kummer A, Dias FMV, Cardoso F, Teixeira AL. Low frequency of bipolar disorder, dopamine dysregulation syndrome, and punding in Brazilian patients with Parkinson's disease. Rev Bras Psiquiatr 2010;32:1-5.
27. Kummer A, Maia DP, Salgado JV, Cardoso FEC, Teixeira AL. Dopamine dysregulation syndrome in Parkinson's disease: case report. Arq Neuro-Psiquiatr 2006;64:1-5.
28. Avanzi M, Baratti M, Cabrini S, Uber E, Brighetti G, Bonfa F. The thrill of reckless driving in patients with Parkinson's disease: an additional behavioral phenomenon in dopamine dysregulation syndrome: Parkinsonism and Related Disorders 2008; 14: 257-258.
29. Evans AH, Lawrence AD, Potts J, Appel S, Lees AJ. Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson's disease. Neurology 2005;65:1570-1574.
30. Schwingenschuh P, Katschnig P, Saurugg R, Ott E, Bhatia KP. Artistic profession: a potential risk factor for dopamine dysregulation syndrome in Parkinson's disease? Mov Disord 2010;25:493-496.
31. Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 2000;95(Suppl 2):S91-S117.
32. Evans AH, Pavese N, Lawrence AD, et al. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. Ann Neurol 2006;59: 852-858.
33. Thomas A, Bonanni L, Gambi F, Di Iorio A, Onofrij M. Pathological gambling in Parkinson's disease is reduced by amantadine. Ann Neurol 2010; 68:400-404.