Myoclonus and Angiokeratomas in Adult Galactosialidosis

Galactosialidosis is an autosomal recessive lysosomal storage disorder characterized by a combined deficiency of β-galactosidase and α-neuraminidase, due to a defect of another lysosomal protein, cathepsin A. The latter, forms a complex with β-galactosidase and neuraminidase, and protects them against excessive proteolytic degradation. Three clinical phenotypes had been described: a severe early infantile form; a milder late infantile type with minor mental deterioration; and a juvenile/adult form, mainly found in Japan, which is characterized by slowly progressive neurological symptoms, skeletal and eye abnormalities, dysmorphism, angiokeratomas, and long survival.[1] Herein, we report a case of galactosialidosis of the juvenile-adult form in a Peruvian girl with angiokeratoma corporis diffusum (ACD) and myoclonus.

A 24-year-old woman presented a 5-year history of involuntary movements. At age 19, she developed a progressive myoclonic disorder that started in the lower limbs and caused frequent falls. The myoclonus subsequently spreads to other body regions. Five years into the disease, she was almost wheelchair bound, and other activities such as eating and speaking were considerably affected. There were, however, no seizures or cognitive decline.

She was the third child of nonconsanguineous Peruvian parents and had two older sisters, one of which had skin lesions but no abnormal movements. There was no family history of neurological disorders. Further information about ancestor's origins couldn't be obtained, although some oriental features seemed to be present in distant relatives. The patient's developmental milestones were normal and she had a history of anemia and irregular menstrual cycles.

Physical examination revealed densely peppered red macules ranging from 1 to 3 mm on palms (Fig. 1), elbows, knees, oral mucosa, lips, and on thighs and loins in a bathing suit distribution. She had distal transverse reddish bands on her nails and few naevi on her soles. She was short (146 cm) and had course facial features and hypertrichosis. Neurological examination showed mild intellectual dysfunction (IQ, 68), mild sensorineural hearing impairment, and decreased visual acuity. Deep tendon reflexes were brisk. Tone and muscle strength were slightly reduced. She had multifocal, stimulus sensitive myoclonus triggered by action. She had a wide-based-bouncing gait and needed help to walk because of negative myoclonus.

The laboratory tests were all normal except for a mild microcytic anemia. Cerebrospinal fluid examination (including lactate levels) and copper metabolism were normal. She had subclinical hypothyroidism but no elevated antithyroid antibodies. Serum gluten antibodies were within normal range. Ophthalmologic examination revealed myopia, mild optic atrophy, reduced visual acuity but no macular cherry-red spots. The electroencephalogram was normal. Needle electromyography showed myopathic changes with normal nerve conduction velocities. Muscle biopsy was nonspecific. Median nerve somatosensory evoked potentials were enlarged (P25-N33(left/right) = 16/20 μV), but C reflexes were absent. No visceromegaly was found on abdominal ultrasound. Brain MRI revealed no abnormalities except vermian atrophy. Basal ganglia spectroscopy was normal. Histopathological examination of skin lesions showed telangiectasias and angiokeratomas. Angiokeratomas are vascular lesions that can be found isolated in normal individuals, but when they are wide spread, the term ACD is used. ACD constitutes the dermatological hallmark of several inherited lysosomal disorders.[2] In a Giemsa-stained peripheral blood smear, small cytoplasmic vacuoles were observed in the lymphocytes, suggesting a storage disorder. Electron microscopic examination revealed numerous cytoplasmic vacuoles with electron-lucid granular deposits in the endothelial cells of blood vessels, in pericytes (Fig. 2) and fibroblasts. The same characteristic vacuoles were found in the naevus melanocytes. Assays of enzymatic activities in leukocytes showed a marked decrease in β-

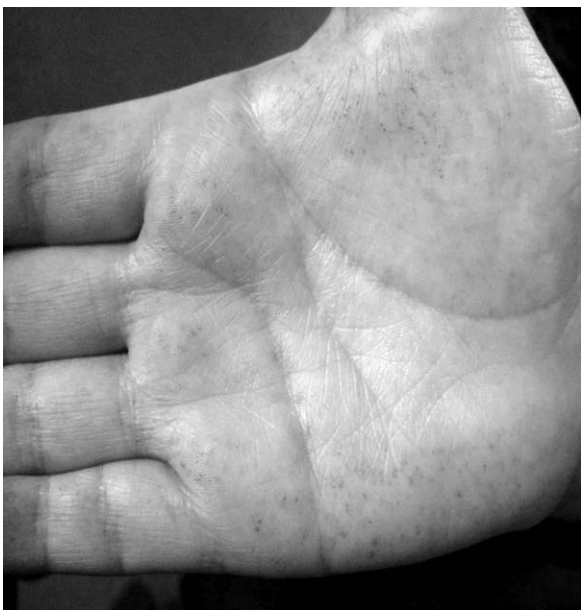

FIG. 1. Telangiectasias on palms.

Additional Supporting Information may be found in the online version of this article.

***Correspondence to:** Luz Abaroa, Department of Neurology, Hospital José M. Ramos Mejía, University of Buenos Aires (UBA), Argentina; luzabaroa@hotmail.com

Relevant conflict of interest: Nothing to report.

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/23500

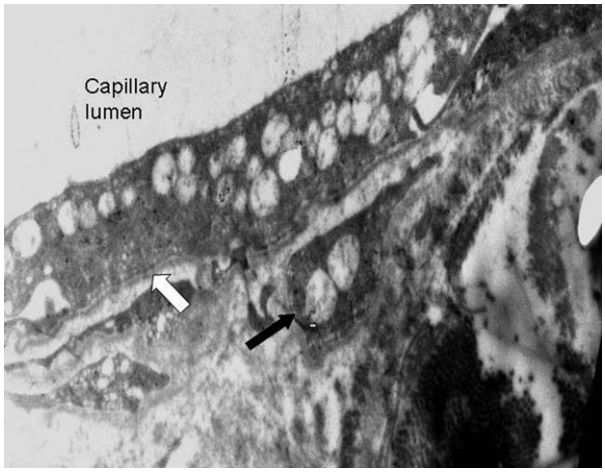

FIG. 2. Electron-microscopic examination showing numerous cytoplasmic vacuoles with electron lucid granular deposits in the endothelial cells and pericytes (arrows).

galactosidase (3.1 umol/l/h; normal range: more than 15). Biochemical analysis showed elevated urinary sialyloligosaccharides characteristic for galactosialidosis.[1]

This case was diagnosed as a juvenile/adult form of galactosialidosis based on biochemical and enzymatic tests. This patient presented with typical features, but so far, she had no epilepsy or macular cherry-red spots also described in this disease.[1,3–5] She was treated with levetiracetam 2,000 mg/day with improvement of myoclonus. Specific therapy in humans is not available at present.[1]

In galactosialidosis, sialyloligosaccharides accumulates in lysosomes of different tissues and are excreted in body fluids. Previous neuropathological studies have demonstrated neuronal swelling and the accumulation of heterogeneous inclusions and cytoplasmic vacuoles in anterior horn cells, spinal ganglia, sympathetic ganglia, myenteric plexus, hippocampus, and Meynert nucleus. Endothelin-1, a substrate of cathepsin A, was more recently identified as one of the storage materials in the cerebellum, hippocampus, and spinal cord.[6]

To date, most of the patients with juvenile galactosialidosis were Japanese[1,3–5] and we think this is the first case reported from Latin America. Conceivably, this young woman has the same genetic mutation as the Japanese subjects perhaps explained by ancient or more recent migration waves arriving in Peru. Alternatively, this patient has a different molecular defect from that seen in the Japanese variant.

Legends to the Video

Segment 1. Action and stimulus sensitive myoclonus is demonstrated. Negative myoclonus interfering with gait improves after treatment. Course facial features can be observed.

Luz Abaroa, MD,[1]* Nelida S. Garretto, MD,[1]
Tomoko Arakaki, MD,[1] Marcelo Kauffman, MD,[1]
Dolores G. Moron, MD,[1] Alex M. Figueredo, MD,[2]
Marina Szlago, MD,[3] and Leo Verhagen Metman, MD[4]

[1]*Department of Neurology, Hospital José M. Ramos Mejía, University of Buenos Aires (UBA), Argentina*
[2]*Department of Dermatology, Hospital José M. Ramos Mejía, University of Buenos Aires (UBA), Argentina*
[3]*Laboratorio de Neuroquímica "Dr. N. A. Chamoles," Fundación para el Estudio de las Enfermedades Neurometabólicas (FESEN), Buenos Aires, Argentina*
[4]*Department of Neurology, Rush University Medical Center, Chicago, USA*

References

1. Johnson WG. β-Galactosidase deficiency: GM1 gangliosidosis, morquio B disease, and galactosialidosis. In: Rosemberg R, Mauro SD, Paulson H, Nestler E, editors. The molecular and genetic basis of neurologic and psychiatric disease. Lippincott Williams & Wilkins, Philadelphia, PA; 2007. p 273–281.
2. Schiller PI, Itin PH. Angiokeratomas: an update. Dermatology 1996;193:275–282.
3. Palmeri S, Hoogeveen AT, Verheijen FW, Galjaard H. Galactosialidosis: molecular heterogeneity among distinct clinical phenotypes. Am J Hum Genet 1986;38:137–148.
4. Nobeyama Y, Honda M, Niimura M. A case of galactosialidosis. Br J Dermatol 2003;149:405–409.
5. Kawachi Y, Matsu-ura K, Sakuraba H, Otsuka F. Angiokeratoma corporis diffusum associated with galactosialidosis. Dermatology 1998;197:52–54.
6. Itoh K, Oyanagi K, Takahashi H, et al. Endothelin-1 in the brain of patients with galactosialidosis: its abnormal increase and distribution pattern. Ann Neurol 2000;47:122–126.

Domestic Violence and Mistreatment in Patients with Parkinsonism: Case Reports, Mechanisms, and Discussion

Domestic violence and other forms of adult mistreatment are a prevalent problem for society. The abuse of older adults has a prevalence of 2–10%.[1] This includes psychological abuse, material exploitation, sexual abuse and neglect, as well as physical harm. Patients with Parkinson's disease (PD) and related disorders are at high risk of abuse. Physical disability, neuropsychiatric complications, and the progressive nature of the disease as they age make them especially vulnerable. There is virtually no commentary in the literature about mistreatment in this patient group. Here, we report two cases of abuse and domestic violence in patients with parkinsonism. The patterns of abuse, risk factors, and outcomes are explored.

The first case was a 74-year-old woman referred to clinic with right upper limb tremor. She also described problems with low mood, anxiety, and urinary continence. She had clinical features indicating idiopathic PD. The letter from the referring practitioner stated that "her tremor gets worse when her husband shouts at her." This prompted an enquiry from the clinic doctor about the patient's relationship with her husband. She then described a history of physical violence and

***Correspondence to:** Alexander M. Thomson, Department of Elderly Medicine, Salford Royal NHS Foundation Trust, Stott Lane, Salford, United Kingdom; alexander.thomson@srft.nhs.uk

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Published online 13 December 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23438

verbal abuse of several years duration. More recently, he had become increasingly aggressive about her movement, describing her as "slow and lazy." The clinic staff offered her options to support her and manage the situation. She declined this and had the mental capacity to do so. The patient was commenced on a dopamine agonist and continues to be monitored with respect to both her PD and her domestic circumstances.

The second case was a 73-year-old woman with a vascular akinetic-rigid syndrome. She had gait ignition difficulties and freezing with levodopa responsiveness. She attended clinic for follow-up. In response to an introductory open question about her recent progress, she immediately raised concerns about her relationship with her husband. A long history of physical and emotional abuse was described. Police involvement 6 months previously had concluded with the patient deciding to allow her husband to return home. Since then he continued blame and humiliate her, citing her physical problems as the cause of his anger. She said he made her feel worthless and felt she was living in an atmosphere of fear. Declining immediate safe placement, she accepted referral to the local Safeguarding Adults team. An investigation was launched and management of her problems is ongoing.

These two cases illustrate ways in which patients with PD and associated conditions are at risk of domestic violence and other forms of abuse. Their physical disability creates both vulnerability and an excuse for the perpetrator of abuse. Patients with cognitive impairment, psychosis, or dementia are also of concern. They may not have the cognitive abilities or resources to identify and manage abuse. If they have challenging behavior, this may fuel retaliation by a second party. Caregivers may choose to withhold dopaminergic medication to prevent physical aggression or wandering in such patients.[2] This form of restraint has not only ethical and moral issues but may also be physically harmful to the patient.[3]

The majority of these patients are elderly. There is a good evidence base highlighting the ways in which older adults are at risk of abuse. Shared living (and therefore increased contact) increases the risk.[4] Social isolation seems to increase the risk of financial abuse (material exploitation).[5] Studies examining the risk factors of victims and abusers consistently indicate that caregiver burden and level of disability are not specifically associated.[1] However, these studies tend to be in general populations, with only some looking at subpopulations (e.g., dementia), with no published work investigating PD alone. There is also significant morbidity and mortality in abused subjects[6] and individuals subject to abuse are more likely to become institutionalized.

Physicians, nurses, and other healthcare workers caring for patients with PD need to be vigilant for incidents of abuse. It is an important governance issue and a marker of quality of care for the local service. This should be supported by appropriate education and training. Local frameworks and processes should be available to support the rapid assessment and management of cases. Intervention by professionals will support patients and contribute positively to their physical and psychological well-being.

Tahir Nazir, MRCP, and Alexander M. Thomson, FRCP*

*Department of Elderly Medicine Salford Royal NHS Foundation Trust, Salford, United Kingdom *E-mail: alexander.thomson@srft.nhs.uk*

References

1. Lachs MS,Pillemer K. Elder abuse. Lance t2004;364:1263–1272.
2. O'Connor KG, Finucane TE. Abuse and neglect of elderly persons. N Engl J Med1995;333:70.
3. Serrano-Duenas M. Neuroleptic malignant syndrome-like or dopaminergic malignant syndrome—due to levodopa therapy withdrawal. Clinical features in 11 patients. Parkinsonism Relat Disord 2003;9:175–178.
4. Lachs MS, Williams C, O'Brien S, HurstL, Horowitz R. Risk factors for reported elder abuse and neglect: a nine-year observational cohort study. Gerontologist1997;37:469–474.
5. Choi NG, Kulick DB, Mayer J. Financial exploitation of elders: analysis of risk factors based on county adult protective services data. J Elder Abuse Neglect 1999;10:39–62.
6. Lachs MS, Williams CS, O'Brien S, Pillemer KA, Charlson ME. The mortality of elder mistreatment. J Am Med Assoc 1998; 280: 428–443.

Interoceptive Sensory Trick for Runner's Dystonia

Task-specific dystonia (TSD), which is characterized by involuntary and sustained muscle contractions of one or more body parts that result in abnormal movements or postures, occurs only during the performance of specific tasks.[1] This disorder has been associated with writers, musicians, and athletes, including runners.[1–4] Mental imagery and sensory tricks have been reported to be effective in ameliorating TSD.[1]

We report the first case of a patient with TSD that involved the neck and trunk during running in which the use of an interoceptive sensory trick with mental imagery led to the amelioration of the patient's symptoms.

A 59-year-old right-handed man was admitted to our department to be evaluated for an abnormal posture that occurred during running. When the patient was 15 years old, he began a training regimen that included running around a track in a counterclockwise direction. Between the ages of 15 and 52 years, the patient performed ~10 hours of training per week. In addition, once per month, the patient regularly participated in a competitive race. At age 53, the patient quit his job and he increased his training to ~25 hours per week. In the following year, he noted an abnormal posture while running that was characterized by a slight lean to his left side. He observed that his trunk and neck tilted to his left side only when he was running. One year before being admitted to our department, the aforementioned abnormal posture was observed even when the patient was walking forwards. The patient's symptoms were evident when he was running and walking forwards or sideways, but he showed no symptoms when he walked backwards,

***Correspondence to:** Keisuke Suzuki, Department of Neurology, Dokkyo Medical University, Tochigi, Japan; keisuke@dokkyomed.ac.jp

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Published online 13 December 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23440

Table 1. Summary of the clinical profiles of patients with Runner's Dystonia

Reference	Case	Patient age (yr)	Onset age (yr)	Gender/ handedness	Prior injury	Family history	Initial involvement	Cumulative years of training before onset	Increase in training the year before onset
Wu and Jankovic [4]	1	40	37	F/L	+	−	Left foot	NA	NA
	2	49	40	F/R	+	−	Left knee	NA	NA
	3	58	46	F/NA	−	−	Left foot	NA	NA
	4	30	20	M/NA	−	−	Left knee	NA	NA
	5	46	44	M/NA	−	−	Right foot	NA	NA
Leveille and Clement [3]	6	57	55	F/NA	NA	+	Left foot	NA	NA
	7	40	30	M/NA	NA	−	Right leg	NA	NA
Present case	8	59	54	M/R	−	−	Neck and trunk	39	Yes

M, male; F, female; R, right handedness; L, left handedness; NA, not available.

sat, or when laying down. The results of a subsequent neurological examination were normal, except for muscle spasms observed in his left pectoralis major muscle. The patient had no previous medical history of psychiatric disease or family history of dystonia. The results of the laboratory analyses, including the measurements of serum ceruloplasmin and copper levels, were normal. There were no Kayser-Fleischer rings noted in the patient's eyes. The brain and whole spine magnetic resonance images failed to reveal any significant abnormalities. In addition, the electroencephalography and cerebral blood flow scintigraphy results were normal.

The symptoms disappeared when the patient held his hands over his head while walking forward. Moreover, it was found that when he ran around the track in a counterclockwise direction, his neck and trunk became tilted to his left side (see video, Segment 1); however, when he ran around the track in a clockwise direction, the orientation of his neck and trunk improved. We subsequently asked the patient to run forward and simultaneously imagine himself running in a clockwise direction, which improved his symptoms (see video, Segment 2). The patient was ultimately diagnosed with TSD related to running.

Although rare, a few athletes have previously been reported to develop task-specific focal dystonias of the legs; however, no previous cases have reported the segmental dystonia reported in this study, particularly during running (see Table 1).[3,4] Similar to the cases reported by Wu et al.,[4] the first observation of dystonic posture in the patient in the present study occurred while the patient was running. In both reports, this posture was consistently observed during running and was also eventually observed while the patients were walking. Similar to the two cases of TSD described by Lo et al.,[5] an interoceptive sensory trick in conjunction with a mental imagery component, in which the patient imagined the normal execution of the target task, was effective in ameliorating our patient's symptoms.

Several cases of paroxysmal exercise-induced dystonia (PED) that involved the legs,[6] and one case that involved the trunk and an arm,[7] that occurred during running have been described; however, PED is unlikely in our case due to the dystonic posture immediately resolving upon cessation of running. In addition, our case had a more task-specific nature and responded to sensory and motor tricks. As a limitation, we cannot completely exclude the possibility of psychogenic movement disorders; however, no evidence of psychiatric disease was found during the examination or in the previous history.

In the present case, the repetitive tilted posture of the neck and trunk to the patient's left side over a 39-year period of running in a counterclockwise direction during training might have played a role in the development of segmental dystonia through a change in cortical plasticity.[1]

Legends to the Video

Segment 1. The patient's neck and trunk leaned to his left side when he ran forwards or ran around a track in a counterclockwise direction.

Segment 2. When we asked the patient to use an interoceptive sensory trick, the patient ran in a normal manner when he ran forwards and simultaneously imagined himself running in a clockwise direction around the track.

Acknowledgments: We wish to thank Dr. Norito Kokubun and Dr. Muneto Tatsumoto for their helpful comments on the patient's diagnosis.

Keisuke Suzuki, MD, PhD,[1]* Naoki Izawa, MD,[1]
Saiko Aiba, MD,[1] Kenichi Hashimoto, MD,[1]
Koichi Hirata, MD, PhD,[1] and
Toshiki Nakamura, MD, PhD[2]

[1]*Department of Neurology, Dokkyo Medical University Tochigi, Japan *E-mail: keisuke@dokkyomed.ac.jp*
[2]*Department of Neurology, Rehabilitation Amakusa Hospital Saitama, Japan*

References

1. Torres-Russotto D, Perlmutter JS. Task-specific dystonias: a review. Ann N Y Acad Sci 2008;1142:179–199.
2. Le Floch A,Vidailhet M, Flamand-Rouviere C, et al. Table tennis dystonia. Mov Disord 2010;25:394–397.
3. Leveille LA, Clement DB. Case report: action-induced focal dystonia in long distance runners. Clin J Sport Med 2008;18:467–468.
4. Wu LJ, Jankovic J. Runner's dystonia. J Neurol Sci 2006;251: 73–76.
5. Lo SE, Frucht SJ. Is focal task-specific dystonia limited to the hand and face? Mov Disord 2007;22:1009–1011.
6. Bhatia KP, Soland VL, Bhatt MH, Quinn NP, Marsden CD. Paroxysmal exercise-induced dystonia: eight new sporadic cases and a review of the literature. Mov Disord 1997;12:1007–1012.
7. Bhattacharyya KB, Basu S, Ray AD, Bhattacharya S. Sporadic paroxysmal exercise induced dystonia: report of a case and review of the literature. Neurol India 2000;48:401–402.

Leptin, Adiponectin, and Resistin Secretion and Diurnal Rhythmicity are Unaltered in Parkinson's Disease

Parkinson's disease (PD) is frequently complicated by unintended weight loss, which often precedes clinical diagnosis and is predominantly due to fat loss.[1] As adipose tissue and release of endocrine factors, so called "adipokines," by fat cells take center stage in the regulation of feeding and body weight,[2] alterations in fat metabolism may partly contribute to weight loss in PD patients. However, single baseline measurements of leptin, the most important adipokine, have yielded conflicting results, showing either unchanged or decreased levels in PD patients.[3–5] Moreover, there are no reports available on leptin secretory dynamics or diurnal variation, and the levels of the two other major adipokines, that is, adiponectin and resistin, have not been assessed so far in PD patients. Given that both leptin and adiponectin have been demonstrated to protect neuronal cells against toxicity induced by 6-hydroxydopamine, 1-methyl-4-phenylpyridinium ion (MPP+) or acetaldehyde, substances used to elicit a PD-like syndrome in animals,[6] it is of crucial importance to settle the issue of whether adipokine secretion is altered in PD patients as this might not only account for weight loss but might also have therapeutic consequences.[6]

We therefore measured 24-hour serum concentrations of the three major adipokines leptin (every 20 min), adiponectin and resistin (every hour) in eight de novo, medication-free PD patients and eight age-, sex-, and fat mass-matched controls (Supporting Information Table 1). The diagnosis of PD was made by a neurologist specialized in movement disorders (R.A.C.R.) according to the UK PD Society Brain Bank criteria. Blood sampling started at 16:30 hours. Three standardized meals were served at 09:00, 13:00, and 19:00 hours. Subjects remained sedentary except for bathroom visits. No daytime naps were allowed. Lights were switched off at 23:00 hours and, the next morning, subjects were awakened at 07:30 hours. Bioelectrical impedance analysis was used to assess fat mass, lean body mass, and fat percentage at 08:00 hours. Serum leptin, adiponectin, and resistin were measured by radioimmunoassay (Linco Research, St. Charles, MO). The coefficients of variation ranged from 3.0 to 5.1% for leptin, 6.3 to 8.1% for adiponectin, and 3.2 to 5.4% for resistin. The detection limits of the assays were 0.5 μg/L for leptin, 1.0 mg/L for adiponectin, and 0.15 μg/L for resistin. Auto-deconvolution and cosinor regression were applied to quantify secretion characteristics of leptin and diurnal variations in leptin, adiponectin, and resistin levels as described previously.[7] Results are expressed as mean ± standard deviation (SD). Unpaired *t*-tests and Spearman's correlation coefficients were calculated to assess intergroup differences and correlations, respectively. All tests were two-tailed and significance level was set at $P < 0.05$.

Mean 24-hour leptin concentrations did not differ significantly between PD patients and controls (12.4 ± 12.2 vs. 15.1 ± 11.5 μg/L, $P = 0.65$; Fig. 1). Basal, pulsatile, and total leptin secretion rates were also not significantly different between the two groups (all $P \geq 0.20$); (Supporting Information Table 2). Similarly, mean 24-hour levels of adiponectin (11.4 ± 6.2 vs. 12.7 ± 4.0 mg/L, $P = 0.62$) and resistin (8.5 ± 2.2 vs. 10.4 ± 4.6 μg/L, $P = 0.30$) did not differ between patients and controls (Supporting Information Fig. 1). Results remained similar when stratified for gender or when expressed per kilogram body fat (data not shown). The acrophases, amplitudes and mesors of leptin, adiponectin and resistin concentration series were also not significantly different between PD and control subjects (all $P \geq 0.12$). Leptin production increased with higher fat mass in both PD patients ($r = +0.98$, $P < 0.001$) and controls ($r = +0.83$, $P = 0.010$). However, neither in patients nor in controls were mean 24-hour adiponectin and resistin levels associated with fat mass (all $P \geq 0.32$). Mean leptin, adiponectin, and resistin levels were not associated with either disease duration or the degree of motor or functional impairment as assessed by the Unified Parkinson's Disease Rating Scale (all $P \geq 0.10$).

This exploratory study provides the first detailed description of leptin secretory dynamics and its diurnal variation, as well as the first description of adiponectin and resistin levels in PD patients. We found no significant differences in the levels or diurnal rhythmicity of leptin, adiponectin, or resistin in de novo PD patients. Our findings therefore suggest that alterations in adipokine secretion are unlikely to account for either weight loss or neurodegeneration in PD. Nevertheless, further studies including PD patients who suffer from weight loss are needed to confirm our findings.

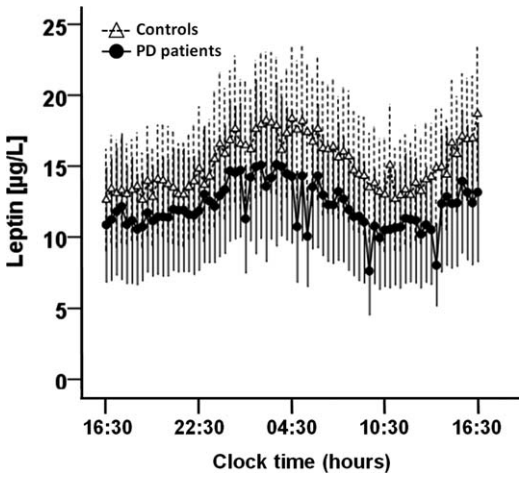

FIG. 1. Mean plasma leptin concentrations in PD patients and matched control subjects. Sampling started at 16:30 hours and was continued at 20-min intervals for 24 hour. Error bars indicate ±1 standard error.

Additional Supporting Information may be found in the online version of this article.

***Correspondence to:** Nasir Ahmad Aziz, Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands; n.a.aziz@lumc.nl

Relevant conflicts of interest/financial disclosures: Nothing to report.
This work was supported by the Netherlands Organization for Scientific Research (017.003.098).
Full financial disclosures and author roles may be found in the online version of this article.

Published online 26 January 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23463

Acknowledgments:s We are greatly indebted to E. J. M. Ladan-Eygenraam, M. van Dijk-Besling, and H. G. Haasnoot-van der Bent for technical support during the study. N.A. Aziz and R.A.C. Roos had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

N. Ahmad Aziz, PhD,[1] Hanno Pijl, MD, PhD,[2]
Marijke Frölich, PhD,[3] Ferdinand Roelfsema, MD, PhD,[2]
Raymund A.C. Roos, MD, PhD[1]

[1]Department of Neurology,
[2]Department of Endocrinology and Metabolic Diseases,
[3]Department of Clinical Chemistry,
Leiden University Medical Center,
Leiden, The Netherlands

References

1. Aziz NA, van der Marck MA, Pijl H, Olde Rikkert MG, Bloem BR, Roos RA. Weight loss in neurodegenerative disorders. J Neurol 2008;255:1872–1880.
2. Trujillo ME, Scherer PE. Adipose tissue-derived factors: impact on health and disease. Endocr Rev 2006;27:762–778.
3. Evidente VG, Caviness JN, Adler CH, Gwinn-Hardy KA, Pratley RE. Serum leptin concentrations and satiety in Parkinson's disease patients with and without weight loss. Mov Disord 2001;16: 924–927.
4. Fiszer U, Michalowska M, Baranowska B, et al. Leptin and ghrelin concentrations and weight loss in Parkinson's disease. Acta Neurol Scand 2010;121:230–236.
5. Lorefalt B, Toss G, Granerus AK. Weight loss, body fat mass, and leptin in Parkinson's disease. Mov Disord 2009;24:885–890.
6. Signore AP, Zhang F, Weng Z, Gao Y, Chen J. Leptin neuroprotection in the CNS: mechanisms and therapeutic potentials. J Neurochem 2008;106:1977–1990.
7. Aziz NA, Pijl H, Frolich M, van der Graaf AW, Roelfsema F, Roos RA. Leptin secretion rate increases with higher CAG repeat number in Huntington's disease patients. Clin Endocrinol (Oxf) 2010;73:206–211.

Mutation and Copy Number Analysis in Paroxysmal Kinesigenic Dyskinesia Families

Paroxysmal kinesigenic dyskinesia (PKD [MIM128200]) is a heritable paroxysmal movement disorder characterized by recurrent and brief attacks of involuntary movements.[1,2] Its family histories show an autosomal dominant inheritance pattern. Our previous linkage and haplotype analyses defined the disease locus on 16p11.2-q12.1,[2] Similarly, other linkage studies of PKD assigned the locus to an overlapping region encompassing the centromere of chromosome 16.[3–5] In our previous study, we performed mutation analysis in seven families on 157 genes between D16S3131 and D16S416 (all the genes within this region); however, we failed to identify the causative gene.[1] Based on many linkage studies, we decided to extend the candidate region until more telomeric locus to D16S503 containing 72 RefSeq genes. Because genomic rearrangement could also result in PKD, we also performed copy number analysis for the entire candidate PKD locus.

Here, we describe the results of mutation analysis in 14 PKD families for the 72 genes between D16S416 and D16S503, and the results of copy number analysis in eight PKD families and two sporadic cases.

We collected 14 Japanese families, PKD-1–PKD-14, each of which includes multiple individuals affected by PKD, and two sporadic cases, PKD-S1 and PKD-S2. Among all these families, 64 patients were diagnosed with PKD. Our previous study showed that all affected members in each family have a disease related haplotype on chromosome 16[1,2] except for PKD-1 and PKD-2, which were not analyzed for haplotype because the family members is small.

Direct sequencing of the 72 genes in the segment between D16S416 and D16S503 revealed two substitutions which were not observed among 288 normal controls and not deposited in dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) (Table 1). A substitution, g.25190C>T (p.R282C) in *GPR114* found in the family PKD-12, was considered as rare variant because it was not co-segregated with PKD. The remaining one was g.35905C>T in exon 4 of *NLRC5* (NM_032206) resulting in p.T153T, segregated with PKD in family PKD-3. Even though this mutation in *NLRC5* is "silent," it might be a pathogenic because of splicing disturbance.[6] However, a nucleotide g.35905C in *NLRC5* is not so highly conserved in other species, and g.35905C>T would not affect splicing by prediction of NNSPLICE (http://www.fruitfly.org/seq_tools/splice.html) and GENSCAN (http://genes.mit.edu/GENSCAN.html; data not shown).

Copy number analysis using HumanExon510S-Duo BeadChip (Illumina, San Diego, CA) showed a deletion in 16p11.2 (Fig. 1A), but this has already been reported in the Database of Genomic Variants (DGV) (http://projects.tcag.ca/variation/). In our previous study, two nonsynonymous substitutions, p.P242T in *SCNN1G* and p.K1063R in *ITGAL*, which were segregated with PKD in one family, were still possible pathogenic mutation for PKD.[1] Structural variants including microdeletions/microduplications within three genes, *ITGAL*, *SCNN1G*, and *NLRC5*, were scanned using array comparative genomic hybridization (aCGH: Agilent Technologies, Santa Clara, CA). Two small deletions not registered in DGV were found within *ITGAL* among several patients (Fig. 1B). However, real-time quantitative PCR revealed genomic alterations in only one PKD patient in the ITGAL region1 and region2 (Fig. 1C). No alteration was found in *SCNN1G* and *NLRC5*. Results of copy number analyses showed no causative copy number changes.

Together with our previous study,[1] we have now analyzed almost all the exons and exon-intron boundaries between

***Correspondence to:** Akira Kinoshita, Department of Human Genetics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; akino@nagasaki-u.ac.jp

Relevant conflicts of interest/financial disclosures: Nothing to report. This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Health, Labour, and Welfare of Japan.
Full financial disclosures and author roles may be found in the online version of this article.

Published online 10 February 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23475

Table 1. Novel SNPs identified in this study

Gene name	Nucleotide change	Location	AA change	Family	Notes
SLC12A3	g.14369C>T	Exon 11	A464A	PKD-13	Synonymous substitution Observed among 96 controls
NUDT21	g.21841T>C	3′UTR		PKD-11, PKD-14	Observed among 96 controls
PLLP	g.4C>T	5′UTR		PKD-13	Observed among 96 controls
KATNB1	g.8648G>A	Exon 3	S58N	PKD-3, PKD-10, PKD-11, PKD-13, PKD-14	Nonsynonymous substitution Observed among 96 controls
	g.15561G>A	IVS5+6		PKD-14	Near the splice site Observed among 96 controls
	g.16858C>T	IVS8+4		PKD-1, PKD-10, PKD-14	Near the splice site Observed among 96 controls
	g.18427C>T	Exon 12	D409D	PKD-1, PKD-13	Synonymous substitution Observed among 96 controls
	g.19491C>T	Exon 14	P472P	PKD-S2	Synonymous substitution Observed among 96 controls
SNORA46[a]	g.122G>A			PKD-8	Observed among 96 controls
	g.128G>A			PKD-4	Observed among 96 controls
NLRC5	g.35905C>T	Exon 4	T153T	PKD-3	Synonymous substitution Not observed among 288 controls
	g.36018C>T	Exon 4	P191L	PKD-11, PKD-12	Nonsynonymous substitution Observed among 96 controls
SLC38A7	g.4673A>G	Exon 3	T10C	PKD-13	Nonsynonymous substitution Observed among 96 controls
	g.13614G>A	Exon 10	Q378Q	PKD-3	Synonymous substitution Observed among 96 controls
GPR114	g.25190C>T	Exon 9	R282C	PKD-12	Nonsynonymous substitution Not observed among 288 controls

[a]*SNORA46* is a noncoding RNA.IVS, intervening sequence; AA, amino acid.

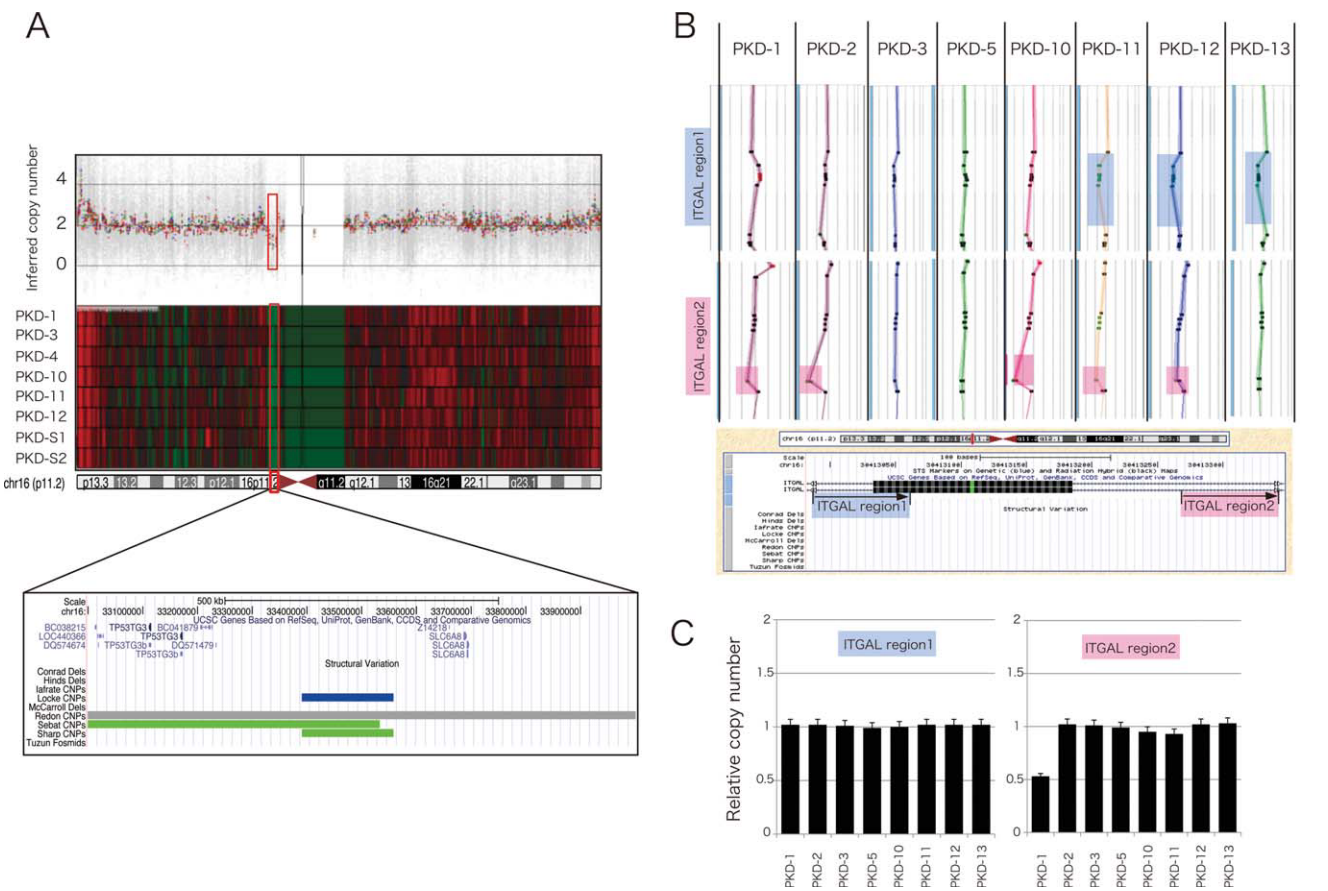

FIG. 1. Copy number analysis in patients with PKD. **A**: Eight patients (PKD-1, PKD-3, PKD-4, PKD-10, PKD-11, PKD-12, PKD-S1, and PKD-S2) are screened for copy number change using HumanExon510S-Duo BeadChip. Representative microarray data for chromosome 16. The region surrounded with a rectangle indicates the deleted region in affected individuals. Three horizontal lines indicate the inferred copy number. The deletion is registered in DGV. **B**: Eight patients (PKD-1, PKD-2, PKD-3, PKD-5, PKD-10, PKD-11, PKD-12, and PKD-13) were screened for copy number change using aCGH. Two microdeleted regions within *ITGAL* detected by array CGH are indicated by gray shaded areas (*ITGAL*, intron 11, Region 1) and light red shaded areas (*ITGAL*, intron 11, Region 2). Array CGH in PKD-11, PKD-12, and PKD-13 showed a ~100 bp loss of copy number in Region 1, and in PKD-1, PKD-2, PKD-10, PKD-11, and PKD-12 showed a ~100 bp loss of copy number in Region 2. **C**: The left and right bar graphs represent the results of quantitative PCR in *ITGAL* Region 1 and Region 2, respectively. No copy number changes were detected in Region 1, and the deletion in Region 2 was detected only in PKD-1, among eight patients with PKD.

D16S3131 and D16S503, but failed to identify the causative gene for PKD. Why have we failed? It is possible that PKD is caused by a recurrent structural aberration beyond the detection level of our experimental approaches. Because the 90th percentile largest gap on the HumanExon510S-Duo BeadChip is 14 kb, it is highly unlikely that our analysis could detect <15 kb structural variants accurately.

The peri-centromeric region (16p11.2–12.1) represents the largest zone of interchromosomal duplications and is composed of ~54 intrachromosomal duplications.[7] It is difficult to find pathogenic copy number changes and base changes in such a complex region. Even though our sequence analysis was comprehensive, some genes could be incomplete. For example, gene conversion in multiple copy number genes would be overlooked in our screening strategy. Furthermore, it is possible that the recurrent or founder intronic mutation cause PKD. den Hollander et al.[8] showed that a recurrent intronic mutation affected the splicing of *CEP290* gene, which resulted in Leber congenital amaurosis. The limitation of our strategy is that most of intronic regions in candidate locus could not be analyzed. We could not have an evidence of founder mutation in Japanese; it is still possible that a founder mutation in an intron is shared in patients.

We conclude that the causative mutation for PKD has not yet been identified. New technologies may be required to identify the PKD mutation in this complex genomic region.

Acknowledgments: We are grateful to the family members for their participation in this study. We thank Ms. Hayashida, Mrs. Oga, and Mrs. Iida for their technical assistance.

Shinji Ono, MD,[1,2] Koh-ichiro Yoshiura, MD, PhD,[1] Naohiro Kurotaki, MD, PhD,[2] Taeko Kikuchi, MD, PhD,[2] Norio Niikawa, MD,[3] and Akira Kinoshita, PhD[1]*

[1]Department of Human Genetics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [2]Department of Psychiatry, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [3]Research Institute of Personalized Health Sciences, Health Sciences University of Hokkaido, Hokkaido, Japan

References

1. Kikuchi T, Nomura M, Tomita H, et al. Paroxysmal kinesigenic choreoathetosis (PKC): confirmation of linkage to 16p11-q21, but unsuccessful detection of mutations among 157 genes at the PKC-critical region in seven PKC families. J Hum Genet 2007;52: 334–341.
2. Tomita H, Nagamitsu S, Wakui K, et al. Paroxysmal kinesigenic choreoathetosis locus maps to chromosome 16p11.2-q12.1. Am J Hum Genet 1999;65:1688–1697.
3. Valente EM, Spacey SD, Wali GM, et al. A second paroxysmal kinesigenic choreoathetosis locus (EKD2) mapping on 16q13-q22.1 indicates a family of genes which give rise to paroxysmal disorders on human chromosome 16. Brain 2000;123:2040–2045.
4. Bennett LB, Roach S, Bowcock AM. A locus for paroxysmal kinesigenic dyskinesia map to human chromosome 16. Neurology 2000;54:125–130.
5. Cuenca-Leon E, Cormand B, Thomson T, et al. Paroxysmal kinesigenic dyskinesia and generalized seizures: clinical and genetic analysis in a Spanish pedigree. Neuropediatrics 2002;33:288–293.
6. Liu W, Qian C, Francke U. Silent mutation induces exon skipping of fibrillin-1 gene in Marfan syndrome. Nat Genet 1997;16: 328–329.
7. Martin J, Han C, Gordon LA, et al. The sequence and analysis of duplication-rich human chromosome 16. Nature 2004;432: 9889–9894.
8. den Hollander AI, Koenekoop RK, Yzer S, et al. Mutations in the CEP290 (NPHP6) gene are a frequent cause of Leber congenital amaurosis. Am J Hum Genet 2006;79:556–561.

Imaging Evidence of Nigral Damage in Dystonia Secondary to Disulfiram Intoxication

There are a few reports on patients who developed dystonia or parkinsonism after disulfiram (DSF) intoxication. Such patients had lesions in the pallidostriatal nucleus on brain magnetic resonance imaging (MRI) studies.[1] However, the integrity of the nigrostriatal dopaminergic neurons has not been studied.

We describe a 25-year-old man who developed generalized dystonia following DSF intoxication. [^{18}F]-FP-CIT brain positron emission tomography (PET) studies showed reduced uptake in the bilateral posterior putamen.

A 25-year-old man presented with generalized dystonia following DSF intoxication. At the age of 15, he committed suicide by taking a 15 g of DSF. When he was transported to the emergency room, he was drowsy but had no focal neurological deficits. One month later, he developed action-induced dystonia in both feet. He also developed sudden onset of transient generalized dystonia. The attacks occurred about 10 times a day and lasted up to 5 min. On neurological examinations, he could understand simple questions and his speech and hand writing were unintelligible. He showed initiation delay in the vertical and horizontal saccadic eye movements. When he stretched out his arms, there was no dystonia. His finger tapping was very slow, but there was no fatigue or akinetic block. Once he made fists, he could hardly release them. While tapping his feet, there was dystonia in the toes. His foot tapping was slow bilaterally, and the amplitude was small. There was no motor weakness or sensory deficit. He needed help to stand and walk due to severe dystonic plantar flexion of the feet. There was a mild spasticity in the legs, but no rigidity in the arms and legs. The knee and ankle jerks increased mildly, but plantar reflexes were flexor bilaterally and there was no ankle clonus. Occasionally, he developed sudden onset of transient generalized dystonia, consisting of retrocollis, upward deviation of the eyes, grasp of the hands, and flexion and

***Correspondence to:** Myung Sik Lee, Department of Neurology, Gangnam Severance Hospital, Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, South Korea; mslee@yuhs.ac

Relevant conflicts of interest/financial disclosures: Nothing to report. This work was supported by a faculty research grant of Yonsei University College of Medicine (grant number 6-2009-0157). Full financial disclosures and author roles may be found in the online version of this article.

Published online 10 February 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23496

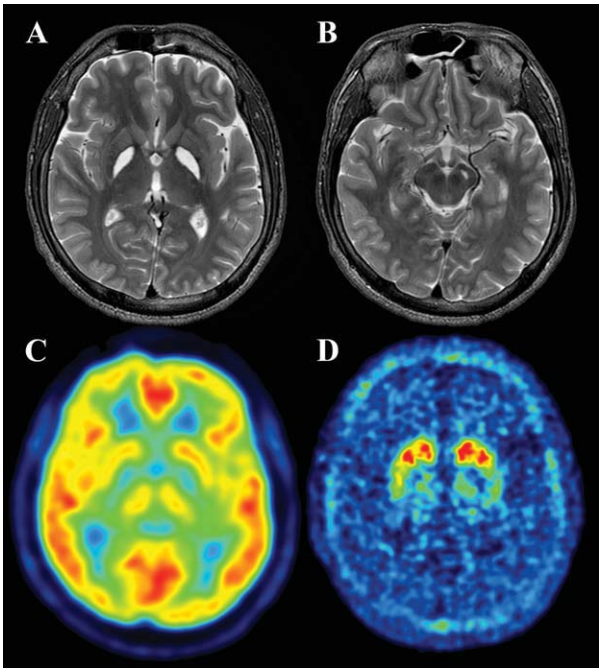

FIG. 1. T2-weighted brain magnetic resonance imaging studies show high signal intensity lesions in the bilateral globus pallidus (**A**) and in the left midbrain (**B**). An [^{18}F]-deoxy glucose brain PET study shows reduced glucose metabolism in the bilateral striatum (**C**). An [^{18}F]-FP-CIT brain PET study shows markedly reduced uptake in the bilateral posterior putamen (**D**).

extension of the extremities (Video). During the attacks, he could not speak and made only teeth grinding noises. Surface electromyography studies showed prolonged co-contraction between agonist and antagonist muscles. Electroencephalography studies during the attack were unremarkable. Results of routine laboratory examinations were all normal. Brain MRI studies showed lesions in the bilateral pallidum (Fig. 1A) and left midbrain (Fig. 1B). [^{18}F]-Deoxyglucose (FDG) brain PET studies showed reduced metabolism in the bilateral striatum (Fig. 1C). [^{18}F]-FP-CIT brain PET studies showed reduced uptake in the bilateral posterior putamen (Fig. 1D). Medical treatment (levodpa 1000 mg and trihexiphenidyl 7.5 mg per day) was ineffective. Botox injection was not effective for the foot dystonia.

DSF intoxication causes damage to the pallidostriatal system.[1] The present case also had lesions in the bilateral pallidum and left midbrain on brain MRI studies and reduced metabolism in the bilateral striatum on FDG PET studies.

In monkeys, DSF induces necrosis in the globus pallidus and substantia nigra pars reticulata but no damage in the substantia nigra pars compacta.[2] However, DSF and its metabolites (CS_2, *N*-diethyldithiocarbamate) inhibit dopamine beta-hydroxylase and consequently increase synaptic dopamine concentration in the striatum. They inhibit superoxide dismutase and reduce glutathione level. Therefore, DSF intoxication may cause severe oxidative stress to the nigral dopaminergic neurons.[3] The patient showed reduced posterior putaminal FP-CIT uptake similar to the pattern observed in Parkinson's disease and MPTP-induced parkinsonian monkeys.

In a review about the movement disorders following basal ganglia lesions, the lentiform nucleus was the most frequent site of the lesion responsible for dystonia.[4] Our case also had lesions in the bilateral lentiform nuclei. He had additional lesion in the nigrostriatal dopaminergic neurons. Isolated nigral lesion may also present with dystonia.[5]

Patients with dystonia following a focal brain lesion frequently develop mobile dystoinc spasm.[4] This case presented with action-induced dystonic spasm and sudden onset of transient dystonia consisted of retrocollis and tonic upward deviation of eyes. Such peculiar phenomenology has been reported in patients with putaminal hemorrhage.[6]

Despite the loss of nigrostriatal dopaminergic terminals, the patient developed no pakinsonian motor deficits. As pallidotomy ameliorates parkinsonian motor deficits, disordered nigrostriatal output in the patient might be blocked by the pallidal lesion before it is delivered to the thalamus.[7] Subclinical damage to the nigrostriatal neurons might be another possible explanation for the absence of parkinsonian motor deficits.

Legend to the Video

A 25-year-old man shows good amplitude but very slow finger tapping. Once he clenches his fists, he can hardly release them. Foot tapping is slow, and the amplitude is small. He shows dystonia in the toe while tapping foot. On standing, he develops severe plantar flexion of both ankles. Occasionally, he develops severe generalized dystonia involving the craniofacial areas, neck, and four limbs.

Yu Na Cho, MD, Chul Hyoung Lyoo, MD, PhD,
Myung Sik Lee, MD, PhD*

Department of Neurology, Gangnam Severance Hospital, Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, South Korea

References

1. Krauss JK, Mohadjer M, Wakhloo AK, et al. Dystonia and akinesia due to pallidoputaminal lesions after disulfiram intoxication. Mov Disord 1991;6:166–170.
2. Meissner W, Prunier C, Guilloteau D, et al. Time-course nigrostriatal degeneration in a progressive MPTP-lesioned macaque model of Parkinson's disease. Mol Neurobiol 2003;28:209–218.
3. Chuang WL, Huang CC, Chen CJ, et al. Carbon disulfide encephalopathy: cerebral microangiopathy. Neurotoxicology 2007;28: 387– 393.
4. Bhatia KP, Marsden CD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 1994;117: 859–876.
5. Lyoo CH, Lee MS. Levodopa responsive hemidystonia associated with contralateral nigral lesion. J Neurol 2010;257:856–857.
6. Shimpo T, Fuse S, Yoshizawa A. Retrocollis and oculogyric crisis in association with bilateral putaminal hemorrhages. Rinsho Shinkeigaku 1993;33:40–44.
7. Peter M, Intemann, BA, Masterman D, et.al. Staged bilateral pallidotomy for treatment of Parkinson disease. J Neurosurg 2001;3: 437–444.

Cervical Dystonia Associated with Facioscapulohumeral Dystrophy: Expanding the Clinical Spectrum?

Dtystonia is a movement disorder characterized by involuntary sustained muscle contraction, resulting in abnormal postures of affected body parts. It is broadly divided in primary and secondary forms. In primary forms, dystonia is the only clinical sign, whereas in secondary forms, a number of other features, such as ataxia, peripheral neuropathy, or parkinsonism may be present.[1] However, excluding mitochondrial diseases, dystonia is rarely associated with myopathy.

Facioscapulohumeral dystrophy (FSHD) is a common muscular dystrophy. It typically presents with weakness of the facial muscles and the stabilizers of the scapula. FSHD is inherited in an autosomal dominant manner and more than 95% of patients carry a deletion of the 3.3 kb tandem repeat D4Z4 on chromosome 4q35. After identification of the genetic defect, a wider clinical spectrum including sensorineuronal hearing loss, epilepsy, and mental retardation has been recognized, suggesting involvement of central nervous system (CNS).[2] However, to our knowledge associated extrapyramidal features have not been described to date.

This 49-year-old woman developed difficulties with lifting up her arms and progressive wasting of shoulder muscles at the age of 30 years. Her mother and two sisters were already diagnosed with FSHD, and genetic diagnosis was subsequently made in her case. Few years later, she developed head shaking. Interestingly, she felt that touching the right cheek helped the head tremor, suggesting a "sensory trick." On examination at the age of 46 years, she had torticollis to the left with head tilt to the right and the elevation of the right shoulder. There was a side to side head tremor and difficulties turning the head to the left, along with typical clinical features of FSHD, including the forward slopping of both shoulders (see Supporting Information Video 1). The diagnosis of cervical dystonia was made. She was investigated to exclude known causes of dystonia and DYT1 mutation, Wilson disease and neuroacanthocytosis were ruled out. Cervical and brain MRI were unremarkable. Since then, she has been regularly treated with botulinum toxin type A injections (Dysport®, Ipsen, UK) in dosages of 150 units into the right splenius, 100 units into the right trapezius, and 75 units into the right sternocleidomastoid, with significant improvement of the dystonia and no worsening of muscular weakness. Until now, neither her mother nor sisters have developed features of dystonia.

We herein report a patient displaying an unusual combination of cervical dystonia and FSHD. Although one may argue that an imbalance of muscle power in the neck, related to the asymmetrical process of muscular atrophy, could be the reason for abnormal head and neck posture in our patient, we consider that the presence of a "sensory trick," and evident overactivity of the affected muscles suggest that there was indeed a dystonic component.

So far, several studies have addressed a possible CNS involvement in FSHD. A study using transcranial magnetic stimulation showed that patients with FSHD may have abnormal intracortical excitability,[3] and a voxel-based morphometry study reported gray matter loss, mainly in frontal lobes.[4] These findings support CNS involvement in FSHD and create a rational basis for speculating on the development of dystonia in FSHD. Pathophysiology of dystonia is not completely understood, but abnormal sensorimotor plasticity is considered to be a key phatophysiological feature.[5] Even though the concurrence of FSHD and cervical dystonia may well be coincidental, it can be hypothesized that reduced afferent input from weak and atrophied muscles favor aberrant sensorimotor plasticity in susceptible FSHD patients, eventually resulting in dystonia. This hypothesis deserves further electrophysiological exploration on a larger sample of patients with FSHD.

Our patient responded well to the botulinum toxin injections in standard dose for cervical dystonia, without worsening of weakness related to FSHD. This demonstrates that even in the presence of muscle disease, botulinum toxin injections may be used with caution to safely treat dystonia.

This case report aims to draw attention on the combination of dystonia and FSHD. If further similar cases are reported, that may support the extrapyramidal involvement in the expanded spectrum of FSHD.

Legend to the Video

Patient exhibits torticollis to the left with head tilt to the right and elevation of the right shoulder. There is a side to side head tremor and difficulties turning the head to the left. These are the features of cervical dystonia. She is unable to turn up the corners of her mouth on smiling, her shoulders tend to slope forward with straight clavicles, and there is bilateral scapular winging. All these are typical findings in FSHD.

Isabel Pareés, MD,[1] Maja Kojovic, MD,[1]
Laxmi V. Prasad Korlipara, MRCP, PhD,[2] and
Kailash P. Bhatia, MD[1]*

[1]*Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, UCL, Queen Square, London, United Kingdom*
[2]*Clinical Neurosciences, Institute of Neurology, UCL, London, United Kingdom*

References

1. Geyer HL, Bressman SB. The diagnosis of dystonia. Lancet Neurol 2006;5:780–790.
2. Padberg GW, Van Engelen BG. Facioscapulohumeral muscular dystrophy. Curr Opin Neurol 2009;22:539–542.

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Kailash P. Bhatia, Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, UCL, Queen Square, London, United Kingdom; k.bhatia@ion.ucl.ac.uk

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Published online 10 February 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23516

3. Di Lazzaro V, Oliviero A, Tonali PA, et al. Changes in motor cortex excitability in facioscapulohumeral muscular dystrophy. Neuromuscul Disord 2004;14:39–45.
4. Quarantelli M, Lanzillo R, Del Vecchio W. Modifications of brain tissue volumes in facioscapulohumeral dystrophy. Neuroimage 2006;32:1237–1242.
5. Quartarone A, Bagnato S, Rizzo V, et al. Abnormal associative plasticity of the human motor cortex in writer's cramp. Brain 2003;126: 2586–2596.

Rasagiline-Induced Serotonin Syndrome

Serotonin syndrome is a dangerous drug-induced condition resulting from an excess of synaptic serotonin and is associated with drugs such as dopamine agonists, tricyclic antidepressants, and selective serotonin reuptake inhibitors.[1] It is usually treated supportively, but complications can include rhabdomyolysis, renal failure, disseminated intravascular coagulation, and ultimately death.[2]

Rasagiline is an irreversible inhibitor of the enzyme monoamine oxidase B (MAO-B) used to treat Parkinson's disease at 1 dose of 1 mg per day. Its pharmacological effect is mediated by an increase in dopamine in the interneuronal synaptic gap.[3] Thus, theoretically, rasagiline can cause serotonin syndrome, but so far there have been no such instances reported, and literature searches (Pubmed and Cochrane Library) have shown no case reports of rasagiline inducing serotonin syndrome. However, our case suggests that rasagiline can do so.

A 76-year-old woman with a 10-year history of Parkinson's disease was started on rasagiline 1 mg/day in clinic, as symptom control was poor on Stalevo100 (carbidopa 25 mg/levodopa 100 mg/entacapone 200 mg) 1 tablet 5 times a day. Her mobility improved on this combination. Four months later she was admitted for a total knee arthroplasty and then transferred to a rehabilitation hospital, where she was mistakenly prescribed rasagiline 1 mg 4 times a day for 4 days until she developed confusion, agitation, and an episode of loss of consciousness. The rasagiline was stopped, and she was transferred to the acute hospital as an emergency.

On admission, she had extreme agitation, pyrexia of 37.7°C, labile blood pressure (between 186/96 and 93/63 mm Hg), and a pulse rate of 100. Neurological examination showed rigidity and a bilateral tremor not typical of her Parkinson's tremor. Cardiovascular, respiratory, and abdominal examinations were otherwise normal. She was not on any antidepressants, and there was no evidence of her having had cheese on her hospital diet card. Blood tests showed a white cell count of 11.5×10^9/L, C reactive protein of 14 mg/L, slightly raised urea of 13.2 mmol/L, and creatinine kinase of 195 U/L. Calcium, liver function tests, and glucose were normal. Chest x-ray and urine culture showed no signs of infection. A CT of the head showed age-related atrophy.

Management was supportive, and she took nearly 4 weeks to improve. After discharge, her agitation and paranoia took weeks to resolve, whereas her confusion remained for some months.

The diagnostic criteria most often used to establish serotonin syndrome are those developed by Sternbach.[4] At least 3 of the following must be present: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. In addition, other possible causes must be excluded, with no recent addition or increase of neuroleptic usage. Competing differential diagnoses include neuroleptic malignant syndrome and malignant hyperpyrexia.[3] Neuroleptic malignant syndrome is precipitated by drugs with dopamine antagonist properties rather than agonist properties. Malignant hyperpyrexia, in contrast, is an inherited condition precipitated by drugs given during general anesthesia.

Our patient had agitation, loss of consciousness, labile blood pressure, tachycardia, fever, and tremor not typical of Parkinson's after a 4-day accidental overdose of rasagaline 4 mg per day. Investigations excluded gastrointestinal bleeding, myocardial infarction, and endocrine and renal abnormalities. Hence, application of the diagnostic criteria makes it plausible that she developed serotonin syndrome.

Rasagiline dosing of 1 mg per day has been established as an effective and well-tolerated dosing schedule in Parkinson's,[5] with trials of up to 20 mg/day in healthy volunteers and up to 4 mg/day in patients without significant adverse effects, with once-daily dosing.[6] However there have never been clinical trials using more than once-a-day dosing with concurrent use of levodopa. Theoretical studies have confirmed that concurrent use could increase the risk of dopamine excess; therefore, recommended doses for adjunctive therapy have been lower than for monotherapy.[7] With appropriately prescribed dosing, serotonin syndrome has not been reported. Rasagiline is known to have a mean steady-state half-life of 3 hours, but in overdose its pharmacological effect is potentiated due to irreversible inhibition of MAO-B. In addition, rasagiline in high dose loses its selectivity for MAO-B, thus increasing serotonin availability.

This combination of irreversible inhibition and loss of selectivity of MAO-B may have precipitated serotonin syndrome in our case. Thus, we would advise careful dosing of rasagiline in adjunctive therapy for Parkinson's disease.

*Correspondence to: Carl Fernandes, Royal Sussex County Hospital, Brighton, United Kingdom; fernandes_c_@hotmail.com

Relevant conflicts of interest/financial disclosures: Nothing to report. Belinda Kessel has been to sponsored meetings by Teva Pharmaceuticals Ltd.
Full financial disclosures and author roles may be found in the online version of this article.

Published online 2 March 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23649

Carl Fernandes, MBBS,[1*] Prashanth Reddy, MRCP[2], and Belinda Kessel, FRCP[3]

[1]*Royal Sussex County Hospital, Brighton United Kingdom;*
[2]*King's College Hospital, London United Kingdom;* [3]*Princess Royal University Hospital Orpington, United Kingdom*

References

1. Isbister GK, Buckley NA. The pathophysiology of serotonin toxicity in animals and humans: implications for diagnosis and treatment. Clin Neuropharmacol. 2005;28:205–214.
2. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust. 2007;187: 361–365.
3. Katzung GB.Basic and Clinical Pharmacology. 10th ed.New York, NY:McGraw-Hill;2007:267.
4. Sternbach H. The serotonin syndrome. Am J Psychiatry. 1991;148: 705–7134.
5. Chen J, Swope D, Dashtipour K. Comprehensive review of rasagiline, a second-generation monoamine oxidase inhibitor, for the treatment of Parkinson's disease. J Clin Ther. 2007;29: 1825–1849.
6. Thebault J, Guillaume M, Levy R. Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type B inhibitor. Pharmacotherapy. 2004;24:1295–1305.
7. Guay D. Rasagiline (TVP-1012): a new selective monoamine oxidase inhibitor for Parkinson's disease. Am J Geriatr Pharmacother. 2006;4:330–346.