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Expansion of the clinicopathological and mutational spectrum of Perry syndrome

Eun Joo Chung [a], Ji Hye Hwang [b], Myung Jun Lee [c], Jeong-Hoon Hong [d], Ki Hwan Ji [a], Woo-Kyoung Yoo [e,f], Sang Jin Kim [a], Hyun Kyu Song [g], Chong S. Lee [b], Myung-Sik Lee [c], Yun Joong Kim [d,f,h,*]

[a] Department of Neurology, Busan Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea
[b] Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[c] Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] ILSONG Institute of Life Science, Hallym University, Anyang, Republic of Korea
[e] Department of Physical and Rehabilitation Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea
[f] Hallym Institute of Translational Genomics & Bioinformatics, Hallym University Medical Center, Republic of Korea
[g] School of Life Sciences and Biotechnology, Korea University, Seoul, Republic of Korea
[h] Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea

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ABSTRACT

Background: Perry syndrome (PS) caused by *DCTN1* gene mutation is clinically characterized by autosomal dominant parkinsonism, depression, severe weight loss, and hypoventilation. Previous pathological studies have reported relative sparing of the cerebral cortex in this syndrome. Here, we characterize novel clinical and neuroimaging features in 3 patients with PS.
Methods: ^{18}F-fluorinated *N*-3-fluoropropyl-2-ß-carboxymethoxy-3-β-(4-iodophenyl) nortropane ([^{18}F]FP-CIT) PET, [^{18}F]fluorodeoxyglucose PET, or volumetric MRI was performed in probands, and imaging data were analyzed and compared with those of control subjects.
Results: We identified 2 novel mutations of *DCTN1*. Oculogyric crisis that presented before levodopa treatment was observed in 1 case. One patient had supranuclear gaze palsy. In 2 cases, [^{18}F]FP-CIT showed marked loss of dopamine transporter binding with only mild parkinsonism. Areas of hypometabolism or cortical thickness change were observed in dorsolateral frontal, anterior cingulate, lateral temporal, and inferior parietal cortices.
Conclusion: Oculomotor manifestations are not uncommon in PS. Neuroimaging studies suggest involvement of the frontotemporoparietal cortex, which may be the clinical correlate of apathy and depression, as well as pathological changes in subcortical structures.

1. Introduction

Perry syndrome (PS; MIM: 68605) is a rapidly progressive neurodegenerative disorder characterized by parkinsonism, central hypoventilation, severe weight loss, and depression or psychiatric symptoms; this disorder is inherited in an autosomal dominant manner [1,2]. Since PS was first described in 2 unrelated Canadian families [3,4], additional families with this syndrome have been identified in different countries (United States [5], France [6], United Kingdom [7,8], Turkey [9], and Japan [10], a Hawaiian family from Japan, and the Fukuoka-4 family [11]). All mutations (G71R, G71E, G71A, T72P, and Q74P) associated with PS are located on exon 2 of the *DCTN1* gene (*dynactin 1*; NM_004082) encoding the p150^{Glued} protein, the major subunit of the dynactin protein complex [2,11]. Previous clinicopathological studies have revealed severe neuronal loss and gliosis in the brainstem and basal ganglia as well as loss of serotonergic neurons in the dorsal raphe nucleus [1,11], whereas cortical regions were usually reported to be unaffected [1,10,12]. In contrast to this, autopsies of a French family [6] exhibited atrophy in the frontal and cingulate cortices, as well as in the ventral tegmental area. A recent report described a case of PS manifesting with behavioral variants of frontotemporal dementia;

* Corresponding author. Hallym Institute of Translational Genomics & Bioinformatics, Hallym University Medical Center, 1605-4 Gwanyang-dong, Dongan-gu, Anyang-si, Gyeonggi-do 431-061, Republic of Korea. Tel.: +82 31 380 1666; fax: +82 31 388 3427.
E-mail address: yunkim@hallym.ac.kr (Y.J. Kim).

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however, the authors did not report any neuroimaging changes except for diffuse cerebral atrophy [13]. Here, we describe 3 PS patients with 2 novel mutations of the *DCTN1* gene who displayed degeneration of frontotemporoparietal cortex documented by 3-dimensional volumetric MRIs or [^{18}F]fluorodeoxyglucose PET ([^{18}F]FDG-PET), accompanied by marked reduction of dopamine transporter binding.

2. Subjects and methods

Informed consents for genetic testing were obtained from each patient.

3. Case reports

3.1. Case #1

A 56 year-old woman who was diagnosed with Parkinson's disease (PD) 2 years ago was transferred to a tertiary referral hospital because of respiratory failure. She had a history of depression. Both her sister and mother, who were diagnosed with PD, had neurogenic respiratory problems and were on ventilators for years before their death. Three years ago, our patient developed a masked face, slurred speech, bradykinesia, rigidity, and gait disturbances, which were resolved with 200 mg of levodopa thrice daily and 0.75 mg of, pramipexole, once daily. She lost approximately 8.5 kg over a 6-month period. Her family did not report any behavioral changes such as disinhibition, perseveration, or violence. She had a history of sudden onset episodic dyspnea that had developed 6 months prior to presentation, but she remained relatively well until she started to experience breathing difficulties while sleeping. An arterial blood gas study in the emergency room revealed marked hypercarbia (pCO_2 = 77 mmHg). On examination, mild bradykinesia and rigidity without tremor were observed. External ocular movements and saccadic movements were normal. OKN was normal. There was no motor weakness. Sensory examination was normal. Frontal lobe releasing signs were negative. Her Mini-Mental State Exam score was 23, but she had no impairment of ADL. Serial brain MRIs were unremarkable. [^{18}F]FP-CIT PET showed marked loss of dopamine transporters. In addition, [^{18}F]FDG-PET showed significant glucose hypometabolism in the anterior cingulate cortex, orbitofrontal cortex, pars opercularis of the inferior frontal gyrus, and inferior parietal lobule.

3.2. Case #2

A 51-year-old man was referred to a movement disorder clinic because of parkinsonism and apathy. His first noticeable symptoms were depressed mood, reduced fluency of speech, and insomnia, all which appeared around 43 years of age. From the age of 45 years, he developed bilateral hand tremor followed by rigidity and bradykinesia, which gradually worsened. His family noticed that he was withdrawn and had no interest in either his surroundings or socializing. He lost about 24 kg in 3 years. His family history revealed that his oldest brother died at age 58 and his and youngest sister at age 52; both had parkinsonism. On neurologic examination, he had dysphagia, shallow breath, and severe tachypnea. Both upward and downward vertical saccades were limited; vertical optokinetic nystagmus was absent, but the vertical vestibulocephalic reflex was preserved. His parkinsonian motor symptoms partially responded to levodopa where the motor scores from the Unified Parkinson's Disease Rating Scale improved from 63 to 53 after treatment with levodopa/benserazide (200 mg/50 mg thrice daily). An arterial blood gas study and polysomnography revealed an apnea index of 6.96 (normal < 5) and central hypoventilation with hypoxia. Respiratory monitoring revealed frequent spells of apnea lasting longer than 20 s, and he received a tracheostomy with respiratory supports. Findings of serial brain MRIs were unremarkable, except for diffuse brain atrophy. [^{18}F]FP-CIT PET also showed marked loss of dopamine transporters.

3.3. Case #3

The proband, a 51-year-old man, visited a movement disorder center because of a six month history of intermittent involuntary upward deviation of the eyes. He was on no medication when his involuntary eyeball movement first developed. He complained that an involuntary tonic upward deviation of his eyeballs occurred every 2–3 days, but he could correct his eyeball position voluntarily. He reported that the frequency of the tonic upward deviation decreased to once every 5–6 days after initiation of levodopa treatment, which had been prescribed based on a diagnosis of PD in another hospital. His father died at age 52 with an unknown neurological problem, and his mother died at the age of 59 with heart disease. His younger sister had levodopa-responsive parkinsonism with supranuclear gaze palsy and jaw opening–closing dyskinesia. On examination, he had symmetric bradykinesia, moderate rigidity, and postural instability. There was no tremor. When walking, there was bilateral reduction of arm swing with relatively good stride and cadence. There was no postural instability. Extraocular movements in the interictal phase were unremarkable. In the ictal phase, though visual fixation restored his eyes temporarily to their primary position, his eyes had the tendency to deviate upward, which did not change with distraction or during rapid alternating movements. He could perform saccades and pursuit with full range, but his eyes showed a tendency to deviate upward while performing saccadic movements. Optokinetic nystagmus was not generated in either the vertical or horizontal directions. Frontal lobe releasing signs, including glabellar, snout, and palmomental reflexes, were positive. Muscle power and sensory examinations were normal. Deep tendon reflexes were brisk without ankle clonus. Serial brain MRIs were unremarkable. Twenty-four-hour urine copper levels were within normal range, and there were no Kayser–Fleischer rings. After initiation of levodopa treatment (250 mg), his hand function improved by 39.4% (right) and 36.2% (left), and his gait improved by 17.6% as assessed by the CAPSIT test.

3.4. DCTN1 sequence analysis

After obtaining informed consent from patients and family members, genomic DNA was extracted from peripheral blood leukocytes using a standard method. Polymerase chain reaction was performed as previously described [2], and the sequence was analyzed by ABI3730 (Applied Biosystems, CA). Novel DCTN1 mutations were validated in 120 Korean healthy controls, and in the 1000 Genomes database.

3.5. MR volumetry image analysis

Using a 1.5 T MR scanner (ACS-NT, Philips, Netherlands), T1-weighted 3D MPRAGE images (repetition time = 8.6 ms, echo time = 4.0 ms, flip angle = 8°, acquired matrices = 252 × 250, slice thickness = 1 mm) were obtained from an index case and from 12 age- and sex-matched controls. Image files in DICOM format were analyzed using the FreeSurfer software (v5.0, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA). FreeSurfer is a semi-automated brain morphometry tool. The details of this post-processing sequence have been described elsewhere [14]. Using a general linear model using age as a covariate, we estimated the