Cerebrotendinous Xanthomatosis Patients With and Without Parkinsonism: Clinical Characteristics and Neuroimaging Findings

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Abstract: Parkinsonism in cerebrotendinous xanthomatosis (CTX) is rare. There are no published studies with imaging findings of dopamine transporter using 99mTc-[2-[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-yl] methyl][2-mercaptoethyl] amino ethyl][ amino]-ethanethiolato(3-)-N2,N2,S2,S2 oxo-[R-(exo-exo)] (99mTc-TRODAT-1) SPECT in CTX patients. This report is on the clinical details of five genetically-proven CTX patients (two with and three without parkinsonism). Imaging findings using cranial magnetic resonance (MR) imaging and 99mTc-TRODAT-1 SPECT are also shown. Clinical correlation of neuroimaging findings and clinical presentations was made. A literature review of the clinical and neuroimaging features of eight CTX patients with parkinsonism reported in the English literature is also presented. The parkinsonian features of our two cases and the other eight reported cases occurred before the age of 50 years. The MR imaging study showed variable findings, in which, besides the common diffuse cerebral and cerebellar white matter lesions shown in CTX, several focal brain lesions were also noted. Of the focal lesions, substantia nigra abnormalities were seen only in the two cases with parkinsonism. The 99mTc-TRODAT-1 SPECT study showed different degrees of unilateral or bilateral abnormalities in the striatal binding in both visual and semiquantitative assessments. Parkinsonism can be one of the neurologic presentations of CTX. Even though abnormal findings of the substantia nigra were detected in both of our CTX patients with parkinsonism, basal ganglion lesions have not been uniformly described in MR imaging findings of reported CTX patients with parkinsonism. 99mTc-TRODAT-1 SPECT study can be of value in the detection of striatal involvement, and the study results also suggest pre-synaptic dopamine neuron involvement in CTX patients with parkinsonism. © 2010 Movement Disorder Society

Key words: cerebrotendinous xanthomatosis; parkinsonism; MR imaging; 99mTc-TRODAT-1 SPECT

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX), a rare autosomal recessive lipid storage disease with a wide clinical and molecular heterogeneity, is caused by a deficiency of the mitochondrial sterol 27-hydroxylase (CYP 27).1–6 The genetic defect of CTX is the mutation in the CYP27 gene that maps to the q33-qter interval of human chromosome 2 [3,5,6]. The major clinical
presentations of CTX are juvenile cataracts, tendinous xanthomatosis, and neurological symptoms. Other abnormalities may include osteoporosis with multiple fractures and early atherosclerosis. Of the neurologic presentations, cerebellar ataxia, neurobehavioral disorders, and spasticity of the limbs are common, whereas extrapyramidal symptoms are uncommonly mentioned. In particular, parkinsonism is a rare feature and there are very few reports in literature. 

99mTc-[2-[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo [3,2,1] oct-2-yl] methyl] (2-mercaptoethyl) amino)-ethanethiolato(3-) oxo-[1R-(exo-exo)] (99mTc-TRODAT-1) is a specific tracer developed to bind selectively to dopamine transporters in the brain. Studies with TRODAT-1 single photon emission computed tomography (SPECT) allow an in vivo assessment of the pre-synaptic dopaminergic neuron activity of the brain. 99mTc-TRODAT-1 SPECT is a useful tool for differentiating parkinsonian disorders. In this study, we analyzed the findings of cranial magnetic resonance (MR) imaging and 99mTc-TRODAT-1 SPECT studies of five genetically proven CTX patients (two with and three without clinically evident parkinsonism) and made a correlation with the clinical presentations.

MATERIALS AND METHODS

Patients

Five genetically confirmed CTX patients with an elevated serum cholestanol on presentation, belonging to two families, were enrolled for this study. Their initial serum cholestanol levels ranged from 24.7 to 46.8 ug/ml (normal value = 3.37 ± 1.55 ug/ml). The diagnosis of CTX were made in 1991 (Family I) and 2004 (Family II), respectively. The clinical features and results of biochemical and genetic studies of the three members of Family I have been previously reported. All five patients received chenodeoxycholic acid (CDCA) treatment (750 mg/day) since diagnosis. The clinical data were summarized in Table 1.

Neuroimaging Studies

Cranial MR Imaging Study

Cranial MR imaging was performed using a 3.0T scanner (Excite, GE Medical System, Milwaukee, WI) equipped with echo-planar capability. Structural MR imaging sequences were as follows: (1) axial fast spin-echo T2-weighted image (T2WI) (4200 ms/102 ms/2[TR/TE/NEX]; field of view (FOV), 240 mm × 240 mm; matrix, 320 × 224; and section thickness, 5 mm); (2) axial fluid-attenuated inversion recovery (FLAIR) image (8000 ms/100 ms/2000 ms/1[TR/TE/TI/NEX]; FOV, 240 mm × 240 mm; matrix, 320 × 256; and section thickness, 5 mm); (3) T1 inversion recovery prepared three-dimensional spoiled gradient-recalled acquisition in steady state sequence with parameters of TR 8600 ms, prep time 400 ms, FOV: 240 mm × 240 mm, slice thickness 1 mm.

99mTc-TRODAT-1 SPECT and Region of Interest Analysis

SPECT Methodology. For this examination, all five cases were injected intravenously with a single bolus dose of 740 MBq (20 mCi) of 99mTc-TRODAT-1. Brain SPECT images were obtained 4 hours later using a SIEMENS dural-head camera (e.cam TM signature series) equipped with high-resolution fanbeam collimators. All image data were acquired in a 128 × 128 matrix with a 1.6 zoom through 360° rotation at 3° per frame, for 40 s per angle step. Images were reconstructed using the filtered back-projection reconstruction method with modified Metz filter (power 3.5). Attenuation correction was performed with the first-order Chang’s method. The attenuation coefficient was μ = 0.12/cm in this study.

Visual Assessment of SPECT. For visual assessment of 99mTc-TRODAT-1 striatal uptake, a predefined grading of the images was classified as follows: (0), normal uptake in all regions (right and left caudate and putamen); (1) slight reduction in uptake in any of the four regions; (2) significant reduction in uptake in any of the four regions.

Semiquantitative Assessments of SPECT. Data were collected and analyzed in a standardized form. Regions of interest (ROI) were drawn on the caudate and putamen of each hemisphere on composite images of the six highest basal ganglia activity slices, based on reference to the corresponding MR images. The occipital cortex was also drawn in the same way and served as background areas. The ratio of specific to nonspecific striatal 99mTc-TRODAT-1 binding were calculated as 99mTc-TRODAT-1 binding ratio = (ROI counts – occipital cortex count)/occipital cortex count.

Reported CTX Patients with parkinsonism in the Literature

For a better delineation of Parkinsonian features in CTX patients, the clinical features and neuroimaging...
data of eight other reported CTX patients with parkinsonism reported in literature7–12 were reviewed and compared.

### RESULTS

Aside from the Parkinsonian features, Cases I-1 and I-2 had moderate mental retardation but without depression by the DSM-IV criteria. Their parkinsonian features included mask face, axial and limb rigidity, fine resting tremors in the hands without pill-rolling features, akinesia/bradykinesia, impaired posture reflex, and shuffling gait (video). There were no sleep-related problems in these two cases. For the parkinsonian features, Cases I-1 and I-2 received oral levodopa (300 mg/day) medication, and both cases had a clinical improvement after 1 month’s treatment. However, the akinesia and bradykinesia persisted (video). Their improvements, as assessed with the modified Hoehn-Yahr scale, were from Stage 4 to Stage 3 in Case I-1 and Stage 3 to Stage 2 in Case I-2. After a 10-month follow-up, both cases remained on the same dose of levodopa and CDCA with further improvement of parkinsonism compared to the initial treatment (video). Neither one developed early end-of-dose weaning-off nor peak-dose dyskinesias.

The findings of cranial MR imaging studies of the five enrolled CTX cases are listed in Table 2. Substantial nigra involvement was noted in Cases I-1 and I-2 is shown in Figure 1.

### Results of 99mTc-TRODAT-1 SPECT and Region of Interest Analysis

As shown in Table 1, the visual assessment study showed that all five cases had different degrees of unilateral or bilateral 99mTc-TRODAT-1 radioactivity decrement (Table 1, Figure 2). Semiquantitative analysis showed that Cases I-1 and I-2 had bilateral striatal ratios below the normal range13 while the other three had a borderline decrement in striatal ratio.

### TABLE 2. Findings of brain magnetic resonance imaging studies of the five cerebrotendinous patients

<table>
<thead>
<tr>
<th>Family</th>
<th>Case No</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy</td>
<td>Supratentorial</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Infratentorial</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperintensity lesions</td>
<td>Periventricular white matter</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Thalamus</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cerebral peduncles</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cerebellar white matter</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Substantial Nigra</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Globus Pallidus</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Striatum</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hypointensity lesions</td>
<td>Dentate nucleus</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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The Clinical Characteristics and Neuroimaging Findings of the Eight Reported CTX Cases with parkinsonism

The other eight reported CTX cases in the literature were three men and five women, aged 33–52 years (mean = 44.4) (Table 3). Of these eight cases, onset of parkinsonism was before the age of 50 in at least seven. parkinsonism was characterized by rigidity, akinesia/hypokinesia, and tremor. Neurologic symptoms further included neurobehavioral disorders, spasticity of the limbs, and cerebellar ataxia. Of these eight cases, medication responsiveness was mentioned in six cases, with two responsive to levodopa treatment alone,7,10 one responsive to diphenylpyraline hydrochloride alone,8 two responsive to a combination of levodopa and diphenylpyraline hydrochloride,9 and one responsive to a combination of levodopa and pergolide11. The described neuroimaging findings of these eight cases are listed in Table 3.

DISCUSSION

This is a report on the clinical details and imaging results of five patients with genetically confirmed CTX, two of whom had concomitant parkinsonism. This study revealed that Cases I-1 and I-2, and previously reported CTX patients with parkinsonism had onset of Parkinsonian features before the age of 50 years, and more than 50% of them belonged to the age range of young-onset Parkinson’s disease (PD).20 The exact incidence of parkinsonism in CTX is not known. However, the combination of CTX and parkinsonism is also found in other independent studies, thereby suggesting that parkinsonism is actually one of the neurologic presentations rather than merely a coincidental manifestation of CTX.7,9–11 Therefore, CTX should be considered in the differential diagnosis of patients with early-onset parkinsonism. We also believe that, because of the earlier presence of other neurologic features such as spasticity of the limbs, cerebellar ataxia,
limited joint movement in the involved joints of tendinous xanthoma, osteoporosis-related multiple fractures, and neurobehavioral disorders,\(^1,2\) the parkinsonian symptoms among CTX patients are usually overlooked, and the incidence is underestimated.

Neuro-pathologic studies in CTX reveals widespread changes with minimal central nervous system region involvement, which does not display some form of pathology,\(^1,2,21,22\) and most of these histopathologic features can be reflected in the typical pattern of MR imaging findings. The results of conventional MR imaging studies of our five and the previously reported eight cases showed variable findings. Besides the common diffuse cerebral and cerebellar white matter lesions shown in CTX,\(^2,22,23\) several focal brain lesions were also noted. From our MRI studies, we speculated that abnormalities of the substantia nigra may be strategic lesions associated with the Parkinsonian feature in Cases I-1 and I-2. Although PD is characterized by degeneration of dopaminergic neurons in the pars compacta of the substantia nigra and subsequent loss of dopaminergic input into the striatum, abnormalities in the substantia nigra, striatum and other parts of basal ganglion were not uniformly described in the reported neuropathologic findings of CTX\(^1,2\) and the neuroimaging findings of the reported CTX patients with parkinsonism as listed in Table 3. Therefore, it is conceivable that MR imaging studies can contribute to the diagnosis of Parkinsonian disorders, but methodologic issues still need to be resolved if the functional state of basal ganglion is of concern. For the functional imaging studies of parkinsonism, in vivo neuroreceptor imaging using SPECT or positron emission tomography (PET) has so far been most valuable.\(^24\)

In this study, the dopaminergic function was studied using \(^{99m}\)Tc-TRODAT-1 SPECT. The uptake of this ligand by the presynaptic membrane in the striatum is a measurement of the integrity of the nigral dopaminergic projections. Decreased uptake seen first in the posterior putamen corresponds with the known pattern of dopaminergic cell loss.\(^16,19,25\) A consistent decrease in uptake was noted in our two cases with Parkinsonism (Cases I-1 and I-2) in both visual assessment and semi-quantitative methods. These \(^{99m}\)Tc-TRODAT-1 SPECT study findings suggest that the Parkinsonian features of CTX patients may be related to the presynaptic dopamine neurons involvement.\(^16,19,25\) This is consistent with the result of functional imaging findings of a CTX patient presenting with hemiparkinsonism, reported by Kuwabara et al.\(^8\) Clinically, Cases

### Table 3. Clinical and laboratory data of the eight reported cerebrotendinous xanthomatosis patients with parkinsonism

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age (yr)/Age at parkinsonism onset (yr)</th>
<th>Parkinsonian symptoms</th>
<th>Other neurologic features</th>
<th>MR imaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>M/44/40</td>
<td>Resting tremor, rigidity, mask face, akinesias, gait disturbance</td>
<td>Neurobehavioral disorders, slurred speech, limb spasticity</td>
<td>Lesions in R’t globus pallidus and L’t putamen, cerebellar atrophy, cerebral cortical atrophy with ventricular dilatation</td>
</tr>
<tr>
<td>2(^a)</td>
<td>F/34/&lt; 34</td>
<td>Mask face, akinesias, rigidity</td>
<td>Limb spasticity</td>
<td>Lesions around bilateral dentate nuclei of the cerebellum, no lesion in the basal ganglia and midbrain</td>
</tr>
<tr>
<td>3(^a)</td>
<td>F/46/41–46</td>
<td>Resting tremor, rigidity, hypokinesia</td>
<td>Seizure, neurobehavioral disorders, limb spasticity, cerebellar ataxia</td>
<td>Severe cerebral cortical and pontocerebellar atrophy, lesions in corona radiate, posterior portion of the internal capsule, cerebral peduncle, and midbrain tegmentum</td>
</tr>
<tr>
<td>4(^a)</td>
<td>F/43/38–43</td>
<td>Resting tremor, rigidity, hypokinesia</td>
<td>Seizure, neurobehavioral disorders, limb spasticity, cerebellar ataxia</td>
<td>Severe cerebral cortical and pontocerebellar atrophy, lesions in corona radiate, posterior portion of the internal capsule, cerebral peduncle, and midbrain tegmentum</td>
</tr>
<tr>
<td>5(^a)</td>
<td>F/33/NA</td>
<td>Resting tremor, hypokinesia</td>
<td>Neurobehavioral disorders, epilepsy, limb spasticity, cerebellar ataxia</td>
<td>Mild cerebellar atrophy</td>
</tr>
<tr>
<td>6(^a)</td>
<td>M/52/35</td>
<td>Resting tremor, bradykinesia, rigidity</td>
<td>Slurred speech, dysphagia, limb spasticity, neurobehavioral disorders</td>
<td>Diffuse cerebral, cerebellar and callosal atrophy, lesions in the R’t cerebellar hemisphere, near the dentate nuclei, no lesions in the basal nuclei</td>
</tr>
<tr>
<td>7(^a)</td>
<td>F/51/37</td>
<td>Mask face, tremor, rigidity, bradykinesia, gait disturbance</td>
<td>Neurobehavioral disorders</td>
<td>Cerebellar atrophy, lesions in the cerebellar white matter, no lesions in the basal ganglia</td>
</tr>
<tr>
<td>8(^a)</td>
<td>M/52/NA</td>
<td>Rigidity, posture instability</td>
<td>Neurobehavioral disorders, limb spasticity</td>
<td>Subcortical atrophy of the hemispheres, brainstem and cerebellum, lesions in the cerebellar deep white matter, cerebral peduncles, and anterior region of the pons</td>
</tr>
</tbody>
</table>

M = Male; F = female; yr = years; NA = nonavailable; R’t = right; L’t = left; MR = magnetic resonance

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I-3, II-1, and II-2 had no clinical features of parkinsonism, but they all had borderline abnormalities in $^{99m}$Tc-TRODAT-1 SPECT studies. One possible explanation is that the loss of dopaminergic neurons is not severe enough to become clinically manifest. Further large-scale studies are needed for a better delineation of the findings of $^{99m}$Tc-TRODAT-1 SPECT studies in CTX patients. In the meanwhile, the Parkinsonian symptoms of Cases I-1 and I-2 had a good response to levodopa treatment, and it has also been observed in other reported CTX patients with parkinsonism. Based on variable regimens and results, therapeutic consensus on the Parkinsonian features cannot be pooled and analyzed thoroughly from the reported CTX cases with parkinsonism. The case reported by Grandas et al. shows initial responses to levodopa but is also complicated by early motor fluctuations of the wearing-off type and mild generalized choreatic dyskinesia during the on stage. The motor complications can be attributed to many factors, including age at disease onset or at initiation of therapy, total daily levodopa dose, duration of treatment, and disease progression. Although cholic acid, especially tauroursodeoxycholic acid, possesses protective effects on PD development, Cases I-1 and I-2 still developed Parkinsonian features during long-term therapy with CDCA. There are also studies suggesting a beneficial effect of diphenylpyraline hydrochloride on the Parkinsonian symptoms of CTX patients, but its mechanism of action remains unclear. Therefore, it is difficult to draw a definitive conclusion based on the small number of patients with different therapeutic combinations. In conclusion, parkinsonism can be one of the neurological presentations of CTX, and it is usually overlooked and underestimated because of the earlier presence of other neurological features that dominate the clinical picture. Abnormal MR imaging findings of the substantia nigra detected in both CTX patients with parkinsonism may account for the presynaptic dopaminergic dysfunction since basal ganglia involvement is not evident in structural imaging. Functional neuroimaging studies such as $^{99m}$Tc-TRODAT-1 SPECT can be of value in the detection of striatal involvement, and the study results also suggest presynaptic dopamine neuron involvement in CTX patients with parkinsonism. LEGENDS TO THE VIDEO

The video demonstrates Case I-1's parkinsonism features before and at 1 and 10 months after levodopa treatment. Before treatment, there was shuffling gait with poor postural reflex and imbalance during walk. There was also grasp reflex and cogwheel rigidity. After 1 month, the shuffling gait improved but hypokinesia and bradykinesia with impaired postural reflex during positional changes persisted. After treatment for 10 months, the patient had remarkable improvement in rigidity, hypokinesia, bradykinesia, and postural reflex. The shuffling gait also further improved.

Acknowledgments: The authors want to express their acknowledgement to the patients for participating this project.

Financial Disclosure: This study is supported by grant from Chang Gung Memorial Hospital 860171; all authors have no financial disclosure to make and no conflict of interest to report. Dr. Wen-Neng Chang, Chun-Chih Chang, Chen-Hsien Lu, Yao-Chung Chuang, Nei-Wen Tsai and Chiung-Chih Chang have received grants from national institutes of health in Taiwan and grants from Kaohsiung Chang Gung Memorial Hospital. Chen-San Su, Shu-Hua Huang, Mei-Jen Hsieh, Tai-Long Pan: None.

Authors' Roles: 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique. Chen-San Su: 3A; Wen-Neng Chang; 1A + 2C + 3B; Shu-Hua Huang: 1B + 1C + 2C; Chun-Chih Chang; 1B + 1C + 2A; Tai-Long Pan: 1C; Chen-Hsien Lu: 1A + 2; Yao-Chung Chuang: 1A + 2; Chi-Ren Huang: 1A + 2; Nei-Wen Tsai: 1A + 2; Mei-Jen Hsieh: 1A + 2; Chiung-Chih Chang: 1A + 3A + 3B.

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