Using fiber tractography and diffusion kurtosis imaging to evaluate neuroimaging changes in patients with cerebrotendinous xanthomatosis after stopping chenodeoxycholic acid treatment for three years

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Background: The aim of this study was to use tractography and diffusion kurtosis imaging (DKI) to evaluate cerebral white matter (WM) changes in patients with cerebrotendinous xanthomatosis (CTX) after stopping chenodeoxycholic acid (CDCA) treatment.

Methods: Two siblings with CTX aged 40 and 38 years, respectively, who had been diagnosed with CTX for 16 years were enrolled. They had received CDCA treatment from 2005 until 2015, after which CDCA was no longer available in Taiwan. Serial brain magnetic resonance imaging (MRI) studies were used to record brain changes, and a series of neuropsychiatric tests were used to evaluate cognitive changes 3 years after stopping CDCA treatment.

Results: The conventional MRI studies revealed progressive changes in dentate nuclei and surrounding cerebellar hemispheres, but no obvious changes in cerebral white matter (WM). Tractography captured in 2018 showed a general reduction in fiber density, especially involving frontal lobe fibers, compared to 2015. In addition, the DKI studies performed in 2018 showed a decreased axonal water fraction in diffuse WM structures and increased RadEAD in frontal WM. Comparisons of the neuropsychiatric test results between 2015 and 2018 showed a marked decline in executive function including design fluency, digit backward span and digit forward span, and this cognitive impairment highly suggested frontal lobe dysfunction.

Conclusions: This study may suggest that cerebral tractography and DKI study results can identify changes in cerebral WM in CTX patients shortly after stopping CDCA treatment, and that they may have a better correlation with the results of neuropsychiatric tests.

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At a glance of commentary
Scientific background on the subject
Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive metabolic disorder of bile acid synthesis, resulting in deposition of cholestanol and cholesterol in various organs, especially the central nervous system. Treatment with chenodeoxycholic acid (CDCA) is effective in normalizing the biochemical abnormalities that underlie the pathogenesis of CTX.

What this study adds to the field
After 3-years cessation of CDCA, two siblings of CTX showed progressive change in neuropsychiatric studies and neuroimaging. The design fluency of both cases and digit forward test of Case II declined after stopping CDCA treatment. Both tractography and DKI reveal marked fiber loss of brain tissue, especially frontal area.

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive metabolic disorder of bile acid synthesis caused by mutations of the CYP27A1 gene, resulting in sterol 27-hydroxylase deficiency and subsequent deposition of cholestanol and cholesterol in various organs, especially the central nervous system [1,2]. Clinically, treatment with chenodeoxycholic acid (CDCA) is effective in normalizing the biochemical abnormalities that underlie the pathogenesis of CTX [1–3]. Of the currently available diagnostic tools for CTX magnetic resonance imaging (MRI) is the most important [4,5], and the typical patterns of MRI features reflect the classic histopathologic findings which may prompt a clinical diagnosis. However, because the clinical course of CTX is slow, conventional MRI cannot be used to monitor the treatment response over a short period of time, and changes, especially in cerebral white matter (WM), are usually unremarkable [1–3]. Therefore, in addition to conventional MRI studies, other MRI tools are used in CTX studies [6] such as diffusion imaging, which can provide more detailed information on WM integrity in subtle brain lesions [7]. In the WM of human brains, water diffusion is restricted by myelin, which can result in different degrees of water perfusion between directions along and across fiber alignment [8]. Diffusion tensor imaging (DTI) can be used to characterize the magnitude, degree of anisotropy, and orientation of directional diffusion tractography [9]. The major limitation of DTI is that diffusion occurs in an unrestricted environment with a Gaussian distribution of the diffusion displacement [10], whereas diffusion kurtosis imaging (DKI) assumes that in complex biological tissues, water diffusion acts in a non-Gaussian manner due to intracellular organelles [11]. There are two non-exchanging compartments in WM, the intra-axonal space and extra-axonal space [12]. The axonal water fraction provides a measure of the water volume in the intra-axonal space relative to that in the extra-axonal space, and it can be used as a biomarker of axonal loss [13]. Radial extra-axial diffusivity can be used to evaluate changes in myelin thickness, even in the presence of axonal loss [14]. Therefore, the use of DTI in combination with DKI may add more information about intracellular and extracellular spaces [15].

CDCA has not been available in Taiwan since 2015, and therefore patients with CTX have not received CDCA treatment for more than 3 years. The aim of this study was to use conventional brain MRI, DTI and DKI to evaluate the neuro-imaging features of two CTX siblings 3 years after stopping CDCA treatment, and to correlate these findings with cognitive changes in neuropsychiatric test results.

Material and methods
Basic clinical features of the two CTX siblings
The clinical and laboratory data of the two siblings, aged 40 and 38 years, respectively, were previously reported in our study on parkinsonism in CTX patients (marked as Family II) [16]. The diagnosis of CTX in these two siblings was made in September 2004, and they received CDCA treatment (750 mg/day) from June 2005 until September 2015, after which CDCA was no longer available in Taiwan. The main clinical features assessed in 2015 and 2018 are shown in Table 1. We used the modified Rankin scale [17] to represent their activities of daily living in different time periods (at diagnosis, 2015 and 2018). This study was approved by the Ethics Committee of our hospital.

Neuropsychiatric studies and brain imaging studies
The neuropsychiatric tests and brain imaging of the two siblings were compared against 30 age-matched, education-matched healthy subjects from a normative database. None of the control subjects had a history of neurologic or psychiatric disorders, and all had normal MRI and basic blood test results. Thirty-minute recall of the Chinese Version of the Verbal Learning Test (CVVLT) was used to assess verbal memory ability [18], and a modified Rey–Osterrieth complex figure was used to evaluate visual perception [19]. Executive function assessments included design fluency and digit forward span [20,21]. Thirty age- and educational level-matched controls were included to calculate the mean and standard deviation of each cognitive measure, and the according Z score for each domain was calculated. All statistical analyses were performed using SPSS software (version 24.0 for Mac; SPSS, Chicago, IL).

MRI was performed using a 3.0 T scanner (Excite, GE Medical Systems, Milwaukee, WI) equipped with echo-planar capability. Sequences were obtained as follows: (1) T1 inversion recovery-prepared 3-dimensional spoiled gradient-recalled acquisition in a steady-state sequence: repetition time 8600 ms, preparation time 400 ms, FOV 240 mm × 240 mm, slice thickness 1 mm; (2) fluid attenuated inversion recovery; and (3) diffusion imaging was performed using a single-shot echo-
planar sequence with gradients applied in 61 non-collinear directions. Axial images were acquired using the following parameters: repetition time/echo time/flip angle 9600 ms/62.7 ms/90 for a b value of 1000 s/mm² and repetition time/echo time/flip angle 12,875 ms/83.4 ms/90 for a b value of 3000 s/mm², a 192 x 192 mm field of view, a 128 x 128 matrix and a 4-mm axial slice thickness. For DKI, we used b values of 1000 and 3000 s/mm² including one b0 image for each b value. The total image acquisition time was 40 min. We used b = 3000 diffusion imaging with 61 directions to obtain tractography of the two CTX siblings using ExploreDTI [22]. In this study, we analyzed images obtained in 2015 and 2018.

We obtained fractional anisotropy (FA) and DKI parameters using ExploreDTI [22]. All T1-weighted images were reoriented with the anterior commissure as the origin using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) with MATLAB 9.1 (R2015b) on a personal computer. All raw diffusion-weighted image volumes were registered to the reference b0 image for motion correction. Affine registration was performed between each diffusion-weighted image volume and the reference b0 to correct for eddy current distortion. To correct for echo-planar imaging-induced susceptibility artifacts, skull-stripped b0 images were registered to the reoriented T1-weighted image. The resulting deformation fields were then applied to the diffusion-weighted image volumes to align them with the T1-weighted image. We used Tract Based-Spatial Statistics (TBSS) of Functional MRI of the Brain Diffusion Toolbox (FSL, version 3.3) to perform tract-based spatial statistics [23]. FA images were created by fitting a tensor model to the raw diffusion data using Functional MRI of the Brain Diffusion Toolbox and then brain-extracted using the Brain Extraction Tool [24]. FA data from all of the subjects were then aligned into a common space using the non-linear registration Image Registration Toolkit [26]. A mean FA image was created and thinned to produce a mean FA skeleton. Aligned FA data from each subject were then projected onto this skeleton, and the resulting data were fed into voxel-wise cross-subject statistics. Non-linear warps and skeleton projections were then applied to the other non-FA images, including axonal water fraction and radial extra-axial diffusivity. A t-test was used for voxel-wise statistics for two-group comparisons. Both age and sex were considered as co-variates of no interest to control for possible interference on regional WM. The resulting statistical maps were thresholded at p < 0.05, and corrected at the cluster level for multiple comparisons using a permutation-based approach.

| Table 1 Demographic data of the two cerebrotendinous xanthomatosis siblings. |
|---------------------------------|
| Case I  | Case II  |
| Genetic mutation (CYP27A1) | Heterozygous: 1333C > T (exon 8) and IVS 7+1G > A (intron 7) | Male Diagnosed 2015 * | Female Diagnosed 2015 * |
| Gender | Male | 2015 | 2018 | Male | 2015 | 2018 |
| Age (years) | 24 | 37 | 40 | 23 | 35 | 38 |
| Cholestanol level (µg/mL) | 28.2 | NA | 96.1 | 24.7 | NA | 61.6 |
| Clinical features | | | | | | |
| Cataracts | + | + | + | + | + | + |
| Mental retardation | + | + | + | + | + | + |
| Psychiatric symptoms | + | + | + | - | - | - |
| Achilles tendon xanthoma | + | + | + | + | + | + |
| Ataxia | + | + | + | + | + | + |
| Epilepsy | + | + | + | + | + | + |
| Modified Rankin Scale | 1 | 1 | 1 | 1 | 1 | 1 |

Abbreviations: NA: none available.
*Both cases discontinued chenodeoxycholic acid treatment in 2015.

Fig. 1 Z scores between the two cerebrotendinous xanthomatosis siblings and controls in neurocognitive tests in 2015 and 2018. Trends of modified Rey–Osterrieth complex figure tests in Case I and Case II were not consistent. Design fluency showed some decline in both Case I and Case II during 2015–2018. There were prominent declines in 30-min recall of the Chinese Version of the Verbal Learning Test (delay recall) and digit forward in Case II in 2018 compared with these scores in 2015.
Results

The clinical and laboratory data of the different time periods

Table 1 shows the clinical conditions recorded at the time of diagnosis (2004), 2015 and 2018 of the two CTX siblings. The clinical features of the two siblings were similar except that Case I had psychiatric symptoms (anxiety and depression) and epilepsy. Their modified Rankin scale scores did not change and were all scored 1 at the time of diagnosis, 2015 and 2018. The serum cholestanol levels of the two siblings, measured in 2018, were high.

The changes in neuropsychiatric test results in different time periods

Fig. 1 shows the results of neuropsychiatric tests of the two CTX siblings and comparisons with the normal controls. The cognitive status of the two CTX siblings showed a marked decline from 2015 to 2018 in multiple domains including verbal memory and executive function (Fig. 1).

The results of neuroimaging studies in different time periods

Fig. 2 shows the results of serial conventional MRI studies of the two CTX siblings, which revealed progressive changes in dentate nuclei and surrounding cerebellar hemispheres. Nevertheless, the changes in cerebral WM were not obvious. Compared with the tractography captured in 2015, the tractography captured in 2018 showed a general reduction in fiber density, especially involving the frontal lobe fibers (Fig. 3). There was no obvious interval change between 2012 and 2015 with regards to loss of WM (Fig. 3). In addition, reduced uncinate fasciculus fibers were found in Case I, and markedly reduced cerebellar tracts were noted in Case II. In DKI studies (Fig. 4), there was a decrease in axonal water fraction in diffuse WM structures and increase in radial extra-axial diffusivity in frontal WM from 2015 to 2018.

Discussion

The treatment response to CDCA therapy is acceptable, and biomarkers and electrophysiological abnormalities can be
reversed, especially if treatment is started early enough [1–3,25,26]. As shown in Table 1, when being treated with CDCA (10 years, from June 2005 to September 2015), the activities of daily living of the two siblings remained consistent, and they were able to carry out usual activities independently. Their clinical features did not change during the 3 years without CDCA treatment (2015–2018). However, despite the positive therapeutic effect of CDCA on CTX, the neurologic and non-neurologic abnormalities of CTX are known to progress eventually [1–3]. This slow but progressive phenomenon was observed in the neuroimaging findings of the two CTX siblings, which showed progressive changes in dentate nuclei and surrounding cerebellar hemispheres (Fig. 2).

In addition to the predominant cerebellar involvement, frontal and temporal lobe dysfunction are known to be important neuropsychiatric presentations in CTX patients [27,28]. In detailed neuropsychiatric studies, the design fluency score of the two CTX siblings and digit forward test

Fig. 3 Fiber tractography of the two siblings with cerebrotendinous xanthomatosis. 2A, 2B and 2C (Case I) captured on 2012, 2015 and 2018, respectively. 2C, 2D and 2E (Case II) captured on 2012, 2015 and 2018, respectively. Compared with the images captured in 2012 and 2015 (arrows), marked frontal fiber loss (arrow) and cerebellar fiber loss (hollow arrows) are shown in the images captured in 2018. The frontal white matter loss between 2012 and 2015 was not as remarkable as that from 2015 to 2018. Compared with the image captured in 2015, the image captured in 2018 showed a reduction in uncinate fasciculus fibers (arrowhead) in Case I.

Fig. 4 Tract-Based Spatial Statistics (TBSS) results of axonal water fraction (3A and 3B) and radial extra-axial diffusivity (3C and 3D) over the whole brain. Fractional anisotropy was applied to be template and 5000 times randomized t-test were performed. Clusters with significant differences in the siblings with cerebrotendinous xanthomatosis and 30 healthy controls (p < 0.05, multiple corrections at the cluster level). Blue voxels (3A and 3C) represent significant areas in 2015 (still under CDCA treatment), and red voxels (3B and 3D) in 2018 (stopped CDCA for 3 years). The clusters are shown with brain slices of MNI 152 T1 template.
score of Case II declined after stopping CDCA treatment for 3 years (Fig. 1), which may indicate rapid progressive damage of frontal lobe fibers, especially in Case II [29,30]. The performance of verbal memory is also known to be affected by the integrity of frontal fibers [31]. The modified Rey–Osterrieth complex figure test showed no evidence of significant impairment of visuospatial function, indicating that the parieto-occipital fibers were not damaged in contrast to the frontal fibers. However, changes in frontal lobe WM were not observed in the serial neuroimaging studies of the two CTX siblings using conventional MRI studies (Fig. 2). Catarino et al. [6] reported that DTI and tractography were better able to detect neuroimaging changes in CTX patients than conventional MRI studies, and their study results revealed reduced FA and tract density in the cerebellum, and widespread cerebral reductions of FA. The decline in frontal lobe function shown in the neuropsychiatric studies in 2018 in the two CTX siblings may be explained by the tractography study findings, which showed markedly decreased fiber density in the frontal WM (Fig. 3). Compared to the fiber lose in the 3-year period after stopping CDCA treatment (2015–2018), there was relatively limited WM damage in the 3 years prior to stopping CDCA treatment (2012–2015) (Fig. 3). In the tractography study, it was also interesting to find uncinate fasciculus damage in Case I, which may have been related to the presence of psychiatric symptoms in this CTX patient [32]. In Fig. 4, the diffuse axonal water fraction in diffuse WM structures may suggest axonal loss, and the increased radial extra-axial diffusivity in frontal WM may suggest the breakdown of myelin and loss of oligodendrocytes. These findings may suggest the complex pathophysiologic changes of CTX in which both axonal loss and demyelination occur [33,34].

CDCA is still the suggested drug of choice to treat CTX [1,35]. Treatment with CDCA may normalize biochemical and electrophysiological biomarkers, and also progressive increases in cerebellar tract density and cerebral FA [6]. In many countries including Taiwan, there has been a shortage of CDCA. Some countries have since overcome this shortage and resumed CDCA treatment for their CTX patients [1]. However, the shortage of CDCA remains in Taiwan, and CTX patients are still not receiving CDCA treatment. The results of the current study may provide evidence suggesting the need to resume CDCA treatment for CTX patients as quickly as possible in order to prevent the rapid deterioration as shown in the tractography and DKI studies.

There are several limitations to this study. First, the biomarker for CTX, cholestanol, can be normalized after using CDCA treatment, however we did not check the serum level of cholestanol regularly during the therapeutic course (2005–2015) of these two CTX siblings. Therefore, there were no corresponding serum cholestanol levels for each brain MRI finding. Nevertheless, the serum cholestanol levels (Table 1) in 2018 were very high without CDCA treatment. Second, the number of cases was small and only two CTX cases were included. However, we believe that the lack of CDCA treatment is of vital and urgent importance for CTX patients as shown by the neuroimaging findings.

Conclusions

This is the first study to use both tractography and DKI to evaluate the neuroimaging changes in CTX patients who had stopped CDCA treatment for 3 years. The results showed marked fiber loss of brain tissue, even though serial conventional MRI studies did not show marked changes in cerebral WM. The DKI findings suggest the complex pathophysiologic changes in CTX including both axonal loss and demyelination. Although the two CTX siblings could perform simple activities of daily living, subtle cognitive decline was identified in detailed neuropsychiatric studies, and this cognitive decline was correlated to the results of tractography and DKI studies in addition to conventional brain MRI studies.

Ethics approval and consent to participate

Informed consent was obtained from the two CTX siblings, and this study was approved by the Ethics Committee of Kaohsiung Chang Gung Memorial Hospital (IRB No: 201900651B0).

Submission declaration and verification

This work has not been published previously and is not under consideration for publication elsewhere.

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Conflicts of interest

The authors have no financial or ethical conflicts of interest to report.

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