Cerebrotendinous Xanthomatosis with Psychiatric Disorders: Report of Three Siblings and Literature Review

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Cerebrotendinous xanthomatosis (CTX), a rare familial lipid metabolic disease inherited via an autosomal recessive trait, is caused by mutations of the sterol 27-hydroxylase gene. Psychiatric disorders may occur in patients with CTX. In Taiwan, Chang et al presented patients with CTX. However, there has not been a case presented about CTX with psychiatric disorders in Taiwan. We present three siblings in one family with CTX combined with moderate mental retardation. One of the siblings had long-term depressed mood, irritability, poor appetite, insomnia, fatigability, and pessimistic thinking and was diagnosed as dysthymic disorder. After 2.5 years of antidepressant treatment at our outpatient clinic, the depressive symptoms of the dysthymic sibling improved greatly. However, the results of the IQ tests of the three siblings did not change after effective treatments for physical manifestations of CTX. In addition, the authors reviewed the literature of CTX combined with psychiatric disorders. *(Chang Gung Med J 2002;25:334-40)*

Key words: cerebrotendinous xanthomatosis, psychiatric disorders, mental retardation, depression.

Cerebrotendinous xanthomatosis (CTX) was first described by van Bogaert et al.[1] It is a rare lipid metabolic disorder inherited in an autosomal recessive trait and is caused by mutations of the sterol 27-hydroxylase gene.[2]

The biochemical pathogenesis of CTX is linked to increased levels of plasma and tissue cholestanol and defective bile acid synthesis.[3,4] Manifestations of this disease include tendon xanthoma, juvenile cataract, osteoporosis, atherosclerosis, and a variety of neurological dysfunctions including pyramidal signs, cerebellar syndrome, dementia,[5] epilepsy,[6] and peripheral neuropathy.[7]

Psychiatric disorders including catatonia, delusion, hallucination, depression, and mental retardation can occur in patients with CTX.[8,9] In Taiwan, patients with CTX were reported by Chang et al.[10,11] However, there have been no reports of patients diagnosed as CTX with psychiatric disorders in Taiwan. In this paper, the authors present three siblings in one family all of whom were diagnosed with CTX combined with mental retardation. One of the siblings had concomitant dysthymic disorder. The authors also reviewed reports in the literature of patients with CTX combined with psychiatric disorders and discussed predisposing factors of depression in patients with CTX.

CASE REPORT

The patients were three siblings, two females and one male, aged 41 to 48 years. Detailed clinical

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courses, laboratory findings, and the family tree were reported in 1992.[10] This report emphasizes the manifestations of their psychiatric illness. The clinical features are summarized in Table 1.

Case A was a 48-year-old unmarried female who had delayed language and motor development, poor vision, and masses over bilateral Achilles tendons since childhood (Fig 1). She could only do simple housework under the supervision of others. She received a diagnosis of CTX at 37 years old. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) intelligence test showed that full IQ was 49, verbal IQ was 55, and performance IQ was 54. After treatment with 750 mg/day of chenodeoxycholic acid (CDCA), her serum biochemical measurement returned to normal range. However, 14 months after receiving treatment, the results of her WAIS-R test had not changed. She visited our outpatient clinic for psychiatric evaluation in January 1996. Mental status examination showed relevant, coherent speech, euthymic mood, fluent thought stream, and no misperception. She received a psychiatric diagnosis of moderate mental retardation based on the criteria of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

Case B was a 43-year-old unmarried male who was found to have poor learning ability, poor visual acuity since 7 years and ankles masses since he was young. He received a diagnosis of CTX at the age of 32 years. The WAIS-R intelligence test showed that full IQ was 45, verbal IQ was 50, and performance IQ was 50. After treatment with 750 mg/day of CDCA, his serum biochemical measurement returned to normal range, and the results of his WAIS-R test were almost the same 14 months after treatment. He accompanied his sisters to visit our psychiatric clinic in January 1996. Mental status examination revealed relevant, coherent speech, euthymic mood. No delusion or hallucination was

Table 1. The Clinical Manifestations of the Three Siblings with Cerebrotendinous Xanthomatosis

	Case A	Case B	Case C
Gender	Female	Male	Female
Age (years)	44	39	37
Age of diagnosis of CTX	37	32	31
Clinical manifestations			
Cataract	Present	Present	Present
Tendinous xanthoma	Present	Present	Present
Osteoporosis	Present	Present	Present
Renal tubular acidosis	Present	Present	Present
Cerebellar ataxia	Present	Present	Present
Pyramidal signs	Present	Present	Present
Peripheral neuropathy	Present	Present	Present
Plasma sterol level			
Baseline			
Cholesterol*, mmol/L	4.30	3.73	4.69
Cholestanol**, mmol/L	105.80 ¡ 10^{-3}	120.57 ¡ 10^{-3}	97.27 ¡ 10^{-3}
CDCA treatment			
Cholesterol*, mmol/L	4.79	4.51	4.92
Cholestanol**, mmol/L	13.87 ¡ 10^{-3}	8.30 ¡ 10^{-3}	9.55 ¡ 10^{-3}
1st WAIS-R test (1992.1)			
Full/Verbal/Performance IQ	49/55/54	45/50/50	45/50/50
2nd WAIS-R test (1993.3)			
Full/Verbal/Performance IQ	49/55/54	45/50/51	46/53/50
Psychiatric diagnosis	Moderate mental retardation	Moderate mental retardation	Moderate mental retardation and dysthymic disorder

*standard level: 4.30 ¡ 0.83 mmol/L

** standard level: (8.69 ¡ 3.99) ¡ 10^{-3} mmol/L

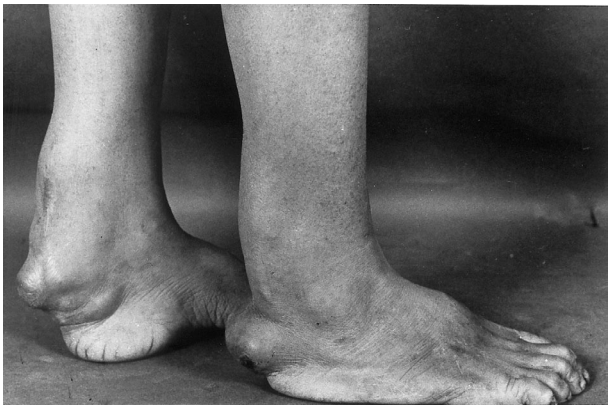

Fig. 1 Thickening of the Achilles tendons and tendinous xanthomas of case A.

detected. He received a psychiatric diagnosis of moderate mental retardation based on DSM-IV criteria.

Case C was a 41-year-old unmarried female who was also found to have delayed developmental milestone and poor learning ability since childhood, and could not work outside the home. She had had poor visual acuity since the age of 6 years and masses in bilateral ankles since the age of 22 years. She was diagnosed as a case of CTX at the age of 31 years. The WAIS-R intelligence test showed that full IQ was 45, verbal IQ was 50, and performance IQ was 50. She received a psychiatric diagnosis of moderate mental retardation based on the DSM-IV criteria. After treatment with the same dose of CDCA as her siblings, her serum biochemical measurement returned to normal range, and the results of her WAIS-R test changed little 14 months after treatment. She visited our psychiatric outpatient clinic for further evaluation in January 1996. According to her father and herself, she had had depressed mood, irritability, pessimistic thinking, difficulty in initiating sleep, crying spells, poor appetite, vague somatic pain, chest tightness and fatigue for 6 years. She visited medical clinics frequently due to a variety of vague somatic discomforts. Case A and Case B bullied her constantly since they were in their teens-they often punched and pinched her. Skin bruises on Case C were noted during physical examination. During mental status examination, she appeared sad, crying, and dressed untidily. She walked with an unsteady, wide-based gait. Her mood was vividly dysphoric and agitated. She murmured "I am dying" repeatedly. She had clear consciousness and no psychotic feature. Hamilton Depression Rating Scale was scored as 24. The score of clinical global impression (CGI) was 5. After being diagnosed as dysthymic disorder, Case C received antidepressant medication (trazodone of 50-150 mg/day), family counseling, and supportive individual psychotherapy for 2.5 years. During the period of outpatient follow up, her depressed and agitated mood improved gradually and somatic complaints decreased at the same time. In August 1999, Hamilton Depression Rating Scale was scored as 14 and the CGI score was 3.

DISCUSSION

The essential features of mental retardation in DSM-IV are "significantly subaverage intellectual functioning, concurrent deficit or impairment in present adaptive functioning with onset before the age of 18".[12] According to the developmental histories and the scores of their IQ, the psychiatric diagnoses of these three siblings should be moderate mental retardation.

There have been some reports of patients with CTX combined with dementia or mental retardation.[9,13] Differential diagnosis between these two psychiatric syndromes is important since mental retardation is generally viewed as a developmental disability, whereas dementia is defined as a chronic degenerative neurological disorder. The diagnosis of dementia can be made any time after the IQ is stationary (usually by the age of 3 or 4 years). However, the diagnosis of dementia is only used when the disorder is not characterized satisfactorily by the diagnosis of mental retardation.[14] Some cases of CTX that occurred during adulthood (older than 18 years) showed mental decline, thus, they were diagnosed with presenile dementia.[8] However, other cases occurred during childhood. They had slow developmental milestone and were diagnosed as mental retardation.[13] Berginer et al (1988) reported two patients with the age of onset were 12 years that were diagnosed with dementia. Possible explanation was the developmental histories of above two cases were normal until the sudden onset of CTX. Our three siblings, who had delayed developmental mile-

stones, were diagnosed with mental retardation, instead of dementia, based on above discussion.

Original articles of CTX have been increasingly published, and most of the recent papers emphasized pathological findings and different modes of gene mutations.[15,16] Nevertheless, few reports have been related to psychiatric disorders. Berginer et al examined 35 patients with CTX and found only four cases (11.4%) with prominent psychiatric symptoms.[8] Auditory hallucination, delusion, catatonia, and aggressive behavior were found among these four cases. Dementia was noted in three cases. After rigorous treatment with neuroleptics (2 cases with haloperidol) and CDCA, these psychiatric symptoms remitted. Only one case required hospitalization to control violent behavior. The authors observed that psychiatric disturbances could occur after the neurological symptoms had improved, before the onset of neurological abnormalities, or even in the absence of dementia. The authors suggested that although the mechanisms leading to psychiatric symptoms in CTX are unknown, the possible pathophysiological factors, like other neurological diseases (including multiple sclerosis and metochromatic leukodystrophy) affecting CNS myelination, related with the processes affecting not only primarily cell bodies, but also functions of neuronal tracts.

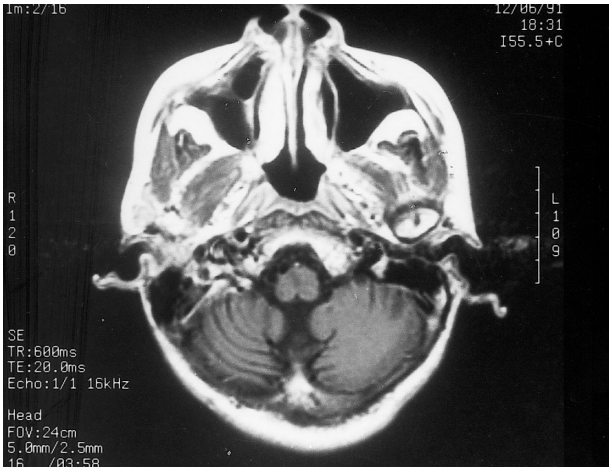

Fig. 2 Cranial MRI of case A showing prominent cerebellar folia (T1 weighted image, SE:TR/TE=600/20ms)

Shapiro presented a patient with CTX comorbid with major depression and dementia. The patient showed signs of agitation, depressed mood, suicidal idea, and deteriorating cognitive functioning. The psychiatric symptoms improved after two periods of hospitalization with medication including antidepressants (doxepin) and neuroleptics (haloperidol). The author highlighted the importance of early detection of the depression and dementia for better outcome.[9] Patients who are mentally retarded may also be depressed, but one needs to rely on precise information from caretakers and thorough observation of symptoms including sad facial expression, psychomotor retardation, irritability, loss of appetite, and affectual volatility to make the diagnosis.[17] In our

Table 2. Psychiatric Disorders of 10 Patients with Cerebrotendinous Xanthomatosis in Four Articles

	Psychiatric Disorders			
Patient	Mental Retardation	Dementia	Depression	Psychosis
Berginer et al[8]				
1	No	Yes	No	Yes
2	No	No	No	Yes
3	No	Yes	No	Yes
4	No	Yes	No	Yes
Farpour et al[13]				
5	Yes	No	No	No
6	Yes	No	No	No
Shapiro[9]				
7	Yes	No	Yes	No
Lee et al				
8	Yes	No	No	No
9	Yes	No	No	No
10	Yes	No	Yes	No

three siblings, only Case C had depressed mood, insomnia, poor appetite, fatigue, agitation, pessimistic thinking, and multiple somatic discomforts for 6 years before visiting the psychiatric outpatient clinic. She was diagnosed as dysthymic disorder and her depressive symptoms responded well to treatments.

Several studies using structural neuroimage techniques, either computed tomography or magnetic resonance imaging (MRI), on patients with CTX showed decreased density and atrophy over the cerebellum.[18] The MRI of our three siblings showed similar findings (Fig 2). Meanwhile, studies revealed the MRI of most depressed patients had ventricular dilatation.[19] The MRI of our three siblings also showed fourth ventricle dilatation. The causal relationship between CTX and depression is not clear. However, genetic disruption of lipid metabolism leading to excessive disposition of cholestanol in the brain tissue might impair development of neural circuit. Thus, impairment in signaling pathways that regulate neuroplasticity and neuronal survival could be associated with cellular pathophysiology of depression.[20] It is not clear why only one, Case C, of our siblings depressed. In addition to the abnormal disposition of cholestanol in brain tissue, the long-term physical abuse by her two elder siblings and her poor coping strategies to stressor may have been predisposing factors of depression.

Altogether, 10 patients in four reports, including our three patients, had CTX with psychiatric syndromes as shown in Table 2. Mental retardation (60%) was the most common, whereas depression (20%) was the least common among these 10 patients. This is the first case report of CTX combined with mental retardation and depression. It is noteworthy to address that not only the neurological and physical disorders of CTX should be treated, but also the reversible psychiatric syndrome of depression should be properly managed.

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腦及肌腱黃瘤症合併精神疾病：三姐弟之個案報告及文獻回顧

李 昱 林博彥 邱念睦 張文能[1] 文榮光

腦及肌腱黃瘤症 (cerebrotendinous xanthomatosis，簡稱CTX) 是一種罕見的家族性體染色體隱性遺傳疾病，是由於 sterol 27-hydroxylase gene 之突變所引起。這種極少見的病症亦可合併精神疾病，此類個案研究在國內雖有張等之報告，但尚不曾有合併精神疾病之報告發表過。茲將介紹一家族中有三姐弟罹患腦及肌腱黃瘤症合併智能不足的病例報告，其中一位病患出現情緒低落，容易哭泣與易怒，且有食慾不振，失眠，疲勞，悲觀想法達六年之久，後來轉介至精神科診斷爲輕鬱症，經過兩年半之追蹤治療，其憂鬱症狀大爲改善，本文並針對CTX合併精神疾病的現象做一文獻回顧。(長庚醫誌 2002;25:334-40)

關鍵字：腦及肌腱黃瘤症，精神疾病，智能不足，憂鬱。

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