

## Cerebrotendinous Xanthomatosis — A Case Report of Two Siblings —

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**= Abstract =** Cerebrotendinous xanthomatosis (CTX), a rare lipid storage disease with diverse neurologic manifestations has, to our knowledge, never been reported in Korea. The authors recently saw two Korean brothers with typical CTX. In the elder one, the clinical presentation included childhood epilepsy, dementia, cataracts, spastic ataxia, and multiple tendon tumefaction in chronological order. In the younger one, dementia, spastic ataxia, and distal muscle atrophy were more pronounced, but tendon enlargement was mild and lenses were intact. In both patients, electroencephalograms, brain CT scans, and MRI scans showed various abnormalities indicating diffuse central nervous system lesions more marked on the cerebellum. Nerve conduction velocity studies revealed peripheral neuropathies. Evoked potential studies were also abnormal, indicating central as well as peripheral conduction defects. Pathologically, the essential features of Achilles tendon biopsies were scattered cholesterol clefts, xanthoma cells, and surrounding granulomatous lesions representing foreign body reactions. The therapeutic response of chenodeoxycholic acid medication was not remarkable.

**Key words:** *Cerebrotendinous xanthomatosis, Sibling study*

### INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare, but well defined recessively inherited disease characterized by xanthomatous deposits in various organs including large tendon, lung, heart, lens, and cerebral white matter. The major clinical features include tendon xanthomas, cataracts, dementia, pyramidal paresis, and cerebellar ataxia (Schimschock *et al.* 1968; Menkes 1975).

Although Schneider (1936) reported the first case of a mentally defective middle aged man, the credit for the first description is generally given to Van Bogaert and his colleagues who more clearly elucidated the clinical and pathological aspects of this disorder.

In 1968, elevated tissue and serum cholestanol (5 $\alpha$ -cholestan-3 $\beta$ -ol) levels were detected by

Menkes and his co-workers. Subsequently, a defect of bile salt production was claimed as a basic mechanism in the pathogenesis, and the deficient enzyme has been sought for in recent investigations (Salen 1971; Setoguchi *et al.* 1974; Salen *et al.* 1979; Oftebro *et al.* 1980).

The abnormalities of brain CT (Berginer *et al.* 1981) and MRI (Swanson and Cromwell 1986) findings were also described recently.

Until 1984, probably less than 30 cases had appeared in the literature (Greenwood *et al.* 1984). The rarity of this disorder prompted us to report following two Korean siblings with clinically and pathologically documented CTX.

### CASE REPORTS

Case 1 A 26 — year — old Korean male was admitted to Seoul National University Hospital because of recurrent seizures associated with progressive mental retardation. His younger brother had



Fig. 1. (patient 1). Both feet show hard, non-tender, massively enlarged Achilles tendons as well as pes cavus deformities.

a similar disease; his parents and two sisters were said to be in good health.

He was born healthy, and vaccinated as scheduled. He had grown up well until age 5 when a generalized seizure first occurred and recurred intermittently thereafter. His mental development worsened so that he needed to attend a special class for the mentally retarded. At age 12, cataracts were noted in both eyes; the vision progressively worsened. By age 21, he was markedly demented and dysarthric. His gait became ataxic. At that time his parents noticed enlarged Achilles tendons on both ankles.

Physical examination- The patient looked dull and apathetic. The scalp hair and eyebrows were thick and coarse. Facial acnes were present on the

forehead. There were no murmurs or arrhythmias heard in the chest. The liver and spleen were not palpable. There was firm, massive enlargement of both Achilles tendons (Fig. 1). Mild pes cavus deformities were also noticed. The tendons of triceps and palmaris longus muscles were also swollen.

Neurological examination- The patient was oriented, but was dementic; he had considerable difficulty with simple calculation and interpretation of proverbs. The name of the current Korean president was correctly identified, but his general fund of knowledge was quite limited. He was severely dysarthric, and the speech was frequently interrupted with long pauses. There were cataracts in both eyes. Visual acuity was 0.1 (right) and 0.04 (left). Ocular movements were full- ranged and conjugate. Other cranial nerves were generally intact, but rapid tongue movement was awkward. Muscle strength was normal, but distal muscles seemed to be slightly atrophic. Sensory perception including position and vibration senses was within normal limits. Deep tendon reflexes were brisk and symmetrical; pathologic reflexes were not elicited. The gait was broad-based and mildly ataxic. Finger-to-nose and heel-to-shin tests demonstrated symmetrical dysmetria of moderate degree.

Laboratory studies- Routine laboratory studies including blood cell count, urine analysis, liver function tests, serum electrolytes, calcium, phosphorous, blood glucose, blood urea nitrogen were all within the normal range. Serum VDRL, hepatitis B surface antigen, antinuclear antibody, rheumatoid factor were all negative. Serum cholesterol and triglyceride levels were within the normal range (195 mg/dl, 126 mg/dl respectively). EKG, chest X-ray, and skull films were normal. Roentgenograms of his ankles showed soft tissue mass densities in the region of the Achilles tendons. An electroencephalogram demonstrated marked abnormality due to nearly continuous high voltage irregular slow waves in all leads. Several medium voltage isolated spikes were seen on the left temporoparietal region. A brain CT scan showed a suspicious low density in the cerebellum, which was more definitely demonstrated by an MRI scan (Fig. 2,3).

Nerve conduction velocities were mildly slowed (32-36 m/sec), and F-wave latencies were prolonged bilaterally in posterior tibial and peroneal nerves. The amplitudes of compound muscle action potentials were also moderately decreased. There were no such changes in the nerves of the

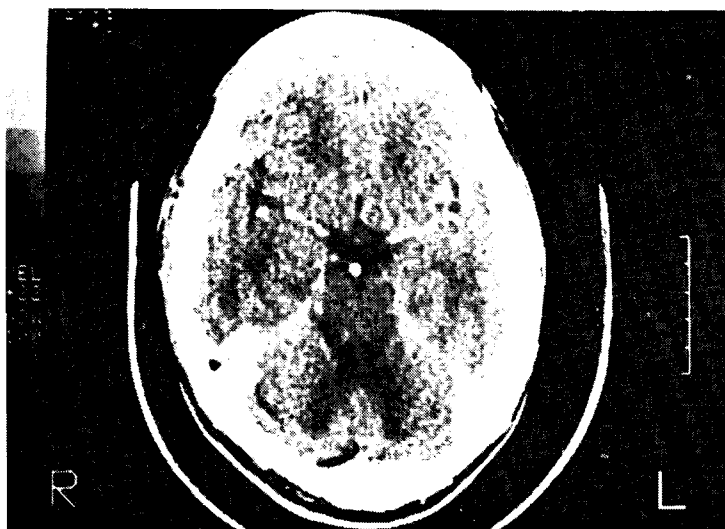


Fig. 2. (patient 1). The CT scan shows hypodense lesions in the cerebellum around the 4th ventricle.



Fig. 3. (patient 1). A T2 weighted MRI reveals definite high-intensity signals in the cerebellar white matter (arrowheads).

upper extremities, and in sural nerves, the conduction velocities were borderline. Evoked potential studies also revealed various abnormalities. In short, brainstem auditory evoked responses showed delayed absolute latencies of wave III, IV, V, and prolonged I-III and I-V interpeak latencies on left ear stimulation, and delayed absolute latencies of all five waves and prolonged I-III and I-V interpeak latencies on right ear stimulation. The median nerve somatosensory evoked potentials showed delayed potentials recorded in ipsilateral Erb's point, C5, and contralateral sensory cortex in both right and left median nerve stimulations. Pattern reversal visual evoked potentials were not performed because of the markedly decreased visual acuity.

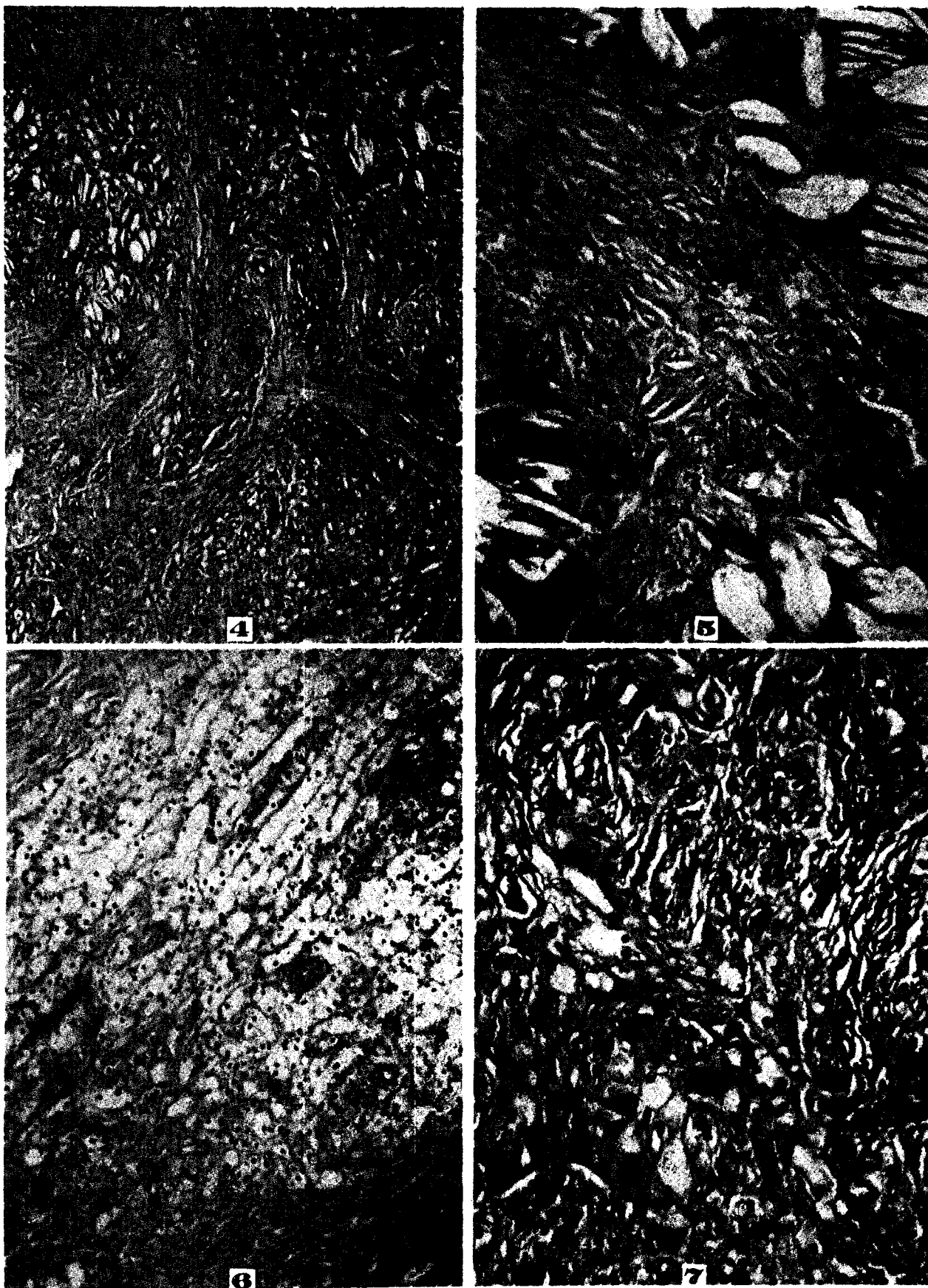
**Pathological examination-** Under the local anesthesia, excision biopsy was undertaken on the left Achilles tendon. Grossly, the tendon was thickened, lobulated, and was yellowish-white. Microscopic examination revealed a dense accumulation of narrow crystalline clefts with granulomatous lesions that contained many large mononuclear cells with foamy cytoplasm and multinucleated giant cells. The clefts appeared to be scattered in clusters throughout the section without any specific relation to blood vessels (Fig. 4,5,6).

**Case 2-** This 24-year-old male patient was the younger brother of the first patient. He suffered from repeated seizures since age 5, and had exhibited an arrest of intellectual development since

then. At age 19, walking difficulty developed and progressively worsened. At age 23, he was confined to a wheelchair because of severe ataxia and paraparesis.

On admission, he was more dementic and more dysarthric than his brother. He rarely spoke even if repeatedly addressed. He did not have cataracts; the visual acuity seemed to be normal. The lower legs were atrophied and muscle strength seemed decreased. Reliable sensory examination was impossible due to the patient's poor cooperation. He had more severe pes cavus deformity and had some degree of scoliosis in the back. The Achilles tendons were thick, but to a lesser degree than his brother's. Deep tendon reflexes were quite brisk; extensor toe signs were elicited bilaterally. Occasional coarse tremor of 4 to 5 Hz was noted on both hands, which was exaggerated on intention.

Routine laboratory findings including serum cholesterol level were within the normal range. An electroencephalogram and a brain CT scan revealed similar but more severe abnormalities compared with his brother's. Nerve conduction velocities were slowed in the nerves of upper limbs as well as those of lower limbs. Brainstem auditory evoked responses showed normal absolute latencies in right and left ear stimulations, but prolonged I-V interpeak latency in left ear stimulation. Somatosensory evoked potential studies showed delayed potentials recorded in Erb's point in both right and



**Fig. 4.** (patient 1). A section of Achilles tendon shows cleft like spaces and adjacent foreign body reaction. Several darkly staining multinucleated giant cells are seen. H&E stain.

**Fig. 5.** High power view of Fig. 4.

**Fig. 6.** In another area, numerous lipid laden xanthoma cells are seen in a cluster.

**Fig. 7.** (patient 2). The Achilles tendon section reveals basically identical feature with Fig. 4, showing clustered foamy cells with adjacent cellular reaction.

left median nerve stimulations. Interpeak latencies between the potentials recorded in Erb's point, C5, and sensory cortex area were within the normal range. Pathological examination of the left Achilles tendon demonstrated basically identical abnormalities compared to his brother's (Fig. 7).

## DISCUSSION

In 1937, Van Bogaert *et al.* described a patient with CTX, and characterized the clinical features as having three stages. The initial stage began in childhood with dementia, and later blended into an adolescent phase characterized by progressive ataxia, spasticity, and cataracts. The third and final stage was characterized by prominent tendon tumefactions, severe spastic ataxic syndromes, progressive bulbar paralysis, and distal muscle wasting. Although cases subsequently reported have enjoyed more variable clinical presentations, the concept of three staged chronological sequence has largely retained its validity until recently (Illingworth and Connor 1987).

Pathologically, the hallmark of this disorder is elevated cholestanol contents in the tissues throughout the body organs including the nervous system, tendons, liver, spleen, adipose tissue and muscles (Menkes *et al.* 1968). Microscopically, large mononuclear cells with foamy cytoplasm, multinucleated giant cells, and fan-shaped collections of crystalline needle-like clefts are characteristically shown. In the nervous system, extensive demyelination is seen as well (Schimschock *et al.* 1968).

The elevated tissue and serum cholestanol levels have triggered recent research on bile salt metabolism in patients with CTX. In 1971, Salen found 10 times more cholestanol and substantial quantities of cholesterol precursors, but virtually no chenodeoxycholic acid in bile secretions of the patients. He suggested overactive hepatic sterol synthesis secondary to a metabolic block in chenodeoxycholic acid production as the basic abnormality in the pathogenesis. The results of *in vivo* as well as *in vitro* experiments of Salen *et al.* (1979) subsequently showed that the site of the enzymatic defect in CTX patients is at the 24 beta-hydroxylation of 5 b-cholestane-3a, 7a, 12a, 25-tetrol. Oftebro *et al.* (1980), however, argued against this, insisting that 26-hydroxylase was the responsible enzyme because its activity was virtually absent in the liver mitochondria of the patients. Whatever enzyme may be responsible, the low concentration of

bile salts produced is currently thought to derepress the normal feedback regulation, thereby overproducing bile salt precursors including cholesterol and its reduced form cholestanol (Swartz *et al.* 1982).

In our cases, the characteristic pathological as well as clinical manifestations are typical of CTX, permitting no alternative diagnosis. The CT and MRI abnormalities also agree fairly well with the findings previously described (Berginer *et al.* 1981; Swanson and Cromwell 1986). Their symptoms (childhood dementia, adolescent spastic ataxia, cataracts, and subsequent tendon tumefaction and bulbar paresis), however, were not equally presented. Mental retardation and gait difficulty were more severe with the younger brother; massively enlarged tendons and cataracts were seen only in the elder one. Unfortunately, serum and tissue cholestanol contents were not measured in our cases.

Several clinical features shown in our cases deserve mention. Both of them suffered from and thus complained chiefly about, the problem of recurrent seizures. In the previously reported cases, seizures were rare and, if present, were not a major problem (Berginer *et al.* 1981). We believe that the differential diagnosis of childhood epilepsy should, therefore, include CTX especially when the victims show evidence of heredity.

Another feature which deserves attention is the fact that both of our patients had peripheral neuropathies confirmed by nerve conduction studies. Peripheral neuropathy had not been recognized as a sign of CTX until 1979, when Kuritzky *et al.* found electrophysiological impairment of the peripheral nerves in all of their four cases. In our cases, the side effect of long term administration of antiepileptic drug (diphenylhydantoin) might have contributed to the development of the peripheral neuropathy. But the atrophic limbs and pes cavus deformities shown in both cases led us to believe that the nerves were more likely damaged by an intrinsic process.

The various abnormalities of evoked potential studies shown here are also of interest. Prolonged absolute latencies of brainstem and somatosensory evoked potentials in both cases are probably attributable to damaged peripheral nerves. Delayed interpeak latencies in brainstem auditory evoked potentials are indicative of brainstem dysfunction in both patients. We think that the latter findings are

unique in that they can be used in the measurement of central conduction delay as well as in the evaluation of therapeutic responses.

As to the prognosis, until recently, CTX has been thought to be universally fatal between the fourth and sixth decade of the patient's life (Schimschock *et al.* 1968; Illingworth and Connor 1987). Some recent work, however, has shed light on the treatment of this malady. As described above, if the defective production of cholic acid and subsequent deregulation of the feedback system is the pathogenesis of this disorder, by adding this end product, the vicious cycle could be terminated. For this purpose, chenodeoxycholic acid or ursodeoxycholic acid were used by some physicians with encouraging results, i.e., decreased serum cholestanol (Berginer *et al.* 1981; Swartz *et al.* 1982). Recently, Berginer *et al.* (1984) tried chenodeoxycholic acid on 17 patients with various neurologic signs. After at least one year of treatment, the majority of them had beneficial effects in the course of the neurological symptoms including dementia, spasticity and peripheral neuropathy.

The clinical and radiological abnormalities of the patients may, to some extent, reflect metabolic encephalopathy and demyelination (due to diffuse cholestanol infiltration) rather than permanent destruction of the brain tissue. This may be the reason why the symptoms of damaged central nervous system are restored in the patients of Berginer *et al.* We also tried chenodeoxycholic acid, 750 mg daily, to our cases. The clinical improvement, however, was not observed in 6 months' of follow up.

## REFERENCES

- Berginer VM, Berginer J, Salen G, Shefer S, Zimmerman RD. Computed tomography in cerebrotendinous xanthomatosis. *Neurology* 1981, 13:89-96
- Berginer VM, Salen G, Shefer S. Long-term treatment of cerebrotendinous xanthomatosis. *N. E. J. M.* 1984, 311:1649-1652
- Greenwood RS, Kahler SG, Aylsworth AS. Inherited metabolic diseases. In Farmer TW (Ed) *Pediatric neurology*, 3rd ed. Harper & Row, Philadelphia, 1984:pp. 366-367
- Illingworth DR, Connor WE. Disorders of lipid metabolism. In Felig P, Baxter JD, Broadus AE, Frohman LA (Ed) *Endocrinology and Metabolism*, 2nd ed. McGraw-Hill, New York, 1987:pp. 1244-1316
- Kuritzky A, Berginer VM, Korczyn AD. Peripheral neuropathy in cerebrotendinous xanthomatosis. *Neurology* 1979, 29:880-881
- Menkes JH. Cerebrotendinous xanthomatosis. In Vinken PJ, Bruyn GW (Ed) *Handbook of Clinical Neurology*. Vol. 10. Elsevier, New York, 1975:pp. 532-541
- Menkes JH, Schimschock JR, Swanson PD. Cerebrotendinous xanthomatosis: the storage of cholestanol within the nervous system. *Arch. Neurol.* 1968, 19:47-53
- Oftebro H, Björkhem I, Skrede S, Schreiner A. Cerebrotendinous xanthomatosis: a defect in mitochondrial 26-hydroxylation required for normal biosynthesis of cholic acid. *J. Clin. Invest.* 1980, 65:1418-1430
- Salen G. Cholestanol deposition in cerebrotendinous xanthomatosis: a possible mechanism. *Ann. Intern. Med.* 1971, 75:843-851
- Salen G, Shefer S, Cheng FW, Dayal B, Batta AK, Tint GS. Cholic acid biosynthesis: the enzyme defect in cerebrotendinous xanthomatosis. *J. Clin. Invest.* 1979, 63:38-44
- Schimschock JR, Alvord Jr. EC, Swanson PD. Cerebrotendinous xanthomatosis: clinical and pathological studies. *Arch. Neurol.* 1968, 18:688-698
- Setoguchi T, Salen G, Tint GS, Mosbach EH. A biochemical abnormality in cerebrotendinous xanthomatosis: Impairment of bile acid biosynthesis associated with incomplete degradation of the cholesterol side chain. *J. Clin. Invest.* 1974, 53:1393-1401
- Schneider C. Über eine eigenartige Hirnerkrankung (vasculäre Lipoidose). *Allg. Z. Psychiat.* 1936, 104:144-163
- Swanson PD, Cromwell LD. Magnetic resonance imaging in cerebrotendinous xanthomatosis. *Neurology* 1986, 36:124-126
- Swartz M, Burman KD, Salen G. Cerebrotendinous xanthomatosis: a cause of cataracts and tendon xanthoma. *Am. J. Med. Sci.* 1982, 283(3):147-152
- Van Bogaert L, Schere HJ, Epstein E. Une forme cerebrale de la cholesterinose generalisee. *Masson et Cie, Paris*, 1937

= 국문초록 =

## 형제에게서 발현된 뇌건성황색종증 2례 보고

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뇌건성황색종증은 다양한 신경학적 징후를 갖는 지질 축적 질환으로서 아직 한국 문헌에는 보고된 적이 없는 것으로 알고있다. 저자들은 최근 형제에게서 발현한 전형적인 증례를 경험하였기에 보고하는 바이다.

26세된 형의 경우, 소아기의 간질, 치매, 백내장 등으로 시작하여 청년기의 강직성, 실조성 운동 장애 및 아킬레스 건을 비롯한 여러 건의 종대를 주된 임상 양상으로 하였으며, 24세된 동생에게서는 치매, 운동 실조 및 원위부 근육 위축 등은 형보다 심하였으나 아킬레스 건 종대는 덜 뚜렷하였고, 백내장은 없었다. 두 환자 모두 뇌파, 뇌 전산화 단층촬영 및 자기 공명 촬영 등에서 다양한 이상 소견을 나타낸바, 소뇌의 병변이 가장 현저하였다. 신경 전도 속도 검사상 말초 신경 장애도 있는 것으로 판단되었으며, 유발 전위검사는 중추 및 말초 신경의 전도 속도 장애를 평가하는데에 유용하였다. 아킬레스 건을 조직 검사한 소견은 콜레스테롤 열(裂), 지질을 포함한 황색종 세포 및 이물질 반응에 기인한 육아종성 조직 등이 특징적이었다. Chenodeoxycholic acid 투여에 대한 임상적 효과는 뚜렷치 않았다.