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Ocular and Systemic Manifestations of Cerebrotendinous Xanthomatosis

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• PURPOSE: Cerebrotendinous xanthomatosis is a storage disease that usually leads to severe mental and neurologic deterioration before the diagnosis and start of treatment are established. We identified major ocular and systemic characteristics that may enable a diagnosis to be made earlier.

• METHODS: Ten patients (group 1) of the University Hospital Nijmegen, with a diagnosis of cerebrotendinous xanthomatosis, were re-examined for detailed ocular and major clinical manifestations. Meanwhile, we looked for similar but undiagnosed cases in patients (group 2) who visited the Institute of Ophthalmology during a 12-month period.

• RESULTS: A diagnosis of cerebrotendinous xanthomatosis had been made in the patients of group 1 at an average age of 40 years (range, 33 to 48 years). Subsequently, six new cases (group 2) were diagnosed in patients 7 to 37 years old (average age, 18 years). Bilateral cataract was the major ocular manifestation in all 16 patients. Small irregular corticonuclear opacities, anterior polar cataracts, and dense posterior subcapsular cataracts were diagnosed at various ages (mean, 18 years; range, 4 to 40 years). Four patients showed clinical signs of optic neuropathy, whereas retinal function was normal in all patients. Other major clinical signs included a history of chronic diarrhea (since childhood), mental deterioration (mean age, 23 years), neurologic deterioration (mean age, 31 years), and tendon xanthomas (mean age, 37 years).

• CONCLUSIONS: Appropriate biochemical investigations for cerebrotendinous xanthomatosis should be performed in patients with unexplained juvenile or early-onset adult cataracts, especially if these cataracts are associated with chronic diarrhea since infancy, mental retardation or deterioration, neurologic dysfunction, or xanthomas.

Cerebrotendinous xanthomatosis is an autosomal recessive sterol storage disease with accumulation of cholestanol and cholesterol in most tissues, in particular, in xanthomas, bile, and brain.1 The disease is caused by a deficiency of hepatic mitochondrial 27-hydroxylase, which is involved in the biosynthesis of bile acids. The gene for this enzyme is on chromosome 2, and mutations in the gene have been described.2 The disease was first reported by van Bogaert, Scherer, and Epstein in 1937.1 The patients they described had dementia, ataxia, and cataracts and showed xanthomas in the tendons and nervous system. The disease is reported to be rare; however, cataract is a common finding.3,4 Cerebrotendinous xanthomatosis results in progressive neurologic and mental deterioration. It is now vitally important to establish the diagnosis at an early age, because treatment with chenodeoxycholic acid has resulted in a favorable biochemical response.5,6,7 In this study, we analyzed the ocular and systemic manifestations of cerebrotendinous xanthomatosis, with special emphasis on the contribu-
tion of the ophthalmologist in the early clinical diagnosis. Attention to the ocular manifestations may improve the recognition of this devastating metabolic disease, which is usually not diagnosed until many years after the initial manifestations.

PATIENTS AND METHODS

In 1990, we started a prospective ophthalmologic examination of ten patients with cerebrotendinous xanthomatosis, which was diagnosed between 1982 and 1989 at the University Hospital Nijmegen. Cerebrotendinous xanthomatosis was confirmed in these patients by gas chromatography of urinary bile alcohols and by determination of cholestanol in blood.2

While we were performing this study and looking for similar patients in our daily practice, six additional cases were diagnosed in 1991. In four of these cases, we recognized the clinical picture by routine ophthalmologic examination and medical history, after which the diagnosis was confirmed biochemically. The two other cases were found by urine examination of siblings. All patients underwent ophthalmologic examination, including testing of best-corrected visual acuity, refraction, external examination, anterior segment slit-lamp microscopy and photography, measurement of intraocular pressure, ophthalmoscopy, echography, elaborate color vision testing, electoretinography, electro-oculography, visual-evoked cortical potentials (with pattern reversal check sizes of 17, 10, and 7 minutes of arc), and Goldmann visual field examination. A detailed medical history was obtained, and previous ophthalmic data were collected from our own records and from records of other ophthalmologists. Main systemic findings were obtained in the Departments of Neurology or Pediatrics during clinical observation of the patients with cerebrotendinous xanthomatosis.

RESULTS

Cerebrotendinous xanthomatosis was established in 16 patients from six unrelated nonconsanguineous Dutch families (Families A, B, C, D, F, and G) and one consanguineous German family (Family E). The major clinical symptoms are summarized in the Table and Figure 1. There were seven male and nine female patients, all of whom had bilateral cataract as an initial sign at a young age (mean, 18 years; range, 4 to 40 years), followed by mental deterioration (mean age, 23 years; range, 4 to 40 years) and neurologic deterioration (mean age, 31 years; range, 15 to 43 years). Two patients were mentally retarded since childhood. Xanthomas were diagnosed only in adults (mean age, 37 years; range, 32 to 43 years), whereas chronic diarrhea had occurred in most patients since childhood.

The mean age at diagnosis of our first ten patients (group 1) was 40 years (range, 33 to 48 years). In two patients (Patients 1 and 5), the diagnosis of cerebrotendinous xanthomatosis was made at necropsy. The mean age at diagnosis of our last six patients (group 2) was 18 years (range, 7 to 37 years). The diagnosis was made much earlier in patients of group 2 than in group 1. The two youngest patients (Patients 11 and 12) were hospitalized elsewhere, because of unexplained diarrhea, before cerebrotendinous xanthomatosis was diagnosed as the cause of associated bilateral cataract.

All 16 patients developed bilateral cataracts before the age of 40 years, and these cataracts were diagnosed before the age of 10 years in seven (44%) patients, and before the age of 20 years in ten (63%) patients. With slit-lamp examination, all lenses showed multiple small opacities, which were more pronounced in the anterior and posterior cortex than in the nucleus (Fig. 2). Four patients had bilateral anterior polar cataract (Fig. 3), in addition to the cortical and nuclear opacities. At the time that vision had reduced markedly, the lenses showed dense posterior subcapsular cataract (Fig. 4). The cataracts progressed to maturity. Ten of the 16 patients underwent cataract surgery (first eye), at an average age of 20 years (range, 7 to 52 years). Four patients (Patients 5, 6, 8, and 12) underwent cataract surgery before age 10 years. At least eight patients (Patients 1, 3, 4–8, and 12) were, or will be, aphakic at age 40 years. In contrast, none of the 14 parents of the 16 patients underwent cataract surgery.

Before cataract surgery, eight patients had spectacles for moderate myopia, and none had spectacles for hypermetropia. With surgical treatment of these cataracts, best-corrected visual acuity of at least 20/40 was attained bilaterally in all patients, except in an
<table>
<thead>
<tr>
<th>PATIENT NO., PEDIGREE, GENDER</th>
<th>AGE AT DEATH</th>
<th>MAJOR SIGNS OF THE SYNDROME</th>
<th>AGE AT WHICH SYMPTOMS WERE DOCUMENTED</th>
<th>AGE AT DIAGNOSIS</th>
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<td>1, A-1, F</td>
<td>48</td>
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TABLE (Continued)

CATARACT AND SYSTEMIC FEATURES OF CEREBROTENDINOUS XANTHOMATOSIS

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<th>PATIENT NO., PEDIGREE, GENDER</th>
<th>AGE AT DEATH (YRS)</th>
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<th>AGE AT WHICH SYMPTOMS WERE DOCUMENTED (YRS)</th>
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<td>Cataract (mild cortical opacities)</td>
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amblyopic eye (Patient 4) and one eye in a patient with unilateral bullous keratopathy (Patient 6). Posterior chamber intraocular lens implantation was uneventful. Mean aphakic refraction was 12.0 diopters (range, 6.0 to 15.5 diopters) in the five patients who had received no intraocular lenses.

Nystagmus and strabismus were relatively rare. Two patients (Patients 5 and 7) had gaze-induced nystagmus. Two patients (Patients 4 and 8) showed exotropia of the left eye. Horizontal corneal diameters were all within normal limits. Corneas were clear, except for a postherpetic corneal leukoma in the right cornea of Patient 2 and a bullous keratopathy after cataract surgery with anterior chamber lens implantation in Patient 6. Bilateral arcus lipoides corneae was present in Patient 8. Bilateral eyelid xanthelasma was present in two patients (Patients 8 and 9), 54 and 51 years old, respectively. One 46-year-old sibling (Family C) showed bilateral eyelid xanthelasma; however, this patient had no clinical or biochemical signs of cerebrotendinous xanthomatosis. Pupillary appearance and reactivity to light were generally normal. Ophthalmoscopic examination of the patients showed no unusual findings, except for some degree of paleness of the optic disks in Patient 1 at age 44 years, Patient 8 at age 54 years, and Patient 13 at age 36 years. Intraocular pressures were within normal limits, except for the left eye of Patient 8.

By echography, axial length measurements in adult patients disclosed no unusual values (average, 23.0 mm; range, 21.5 to 27.5 mm). Electroretinography, electro-oculography, or both, were performed in seven patients and were found to be within normal limits in all examined eyes. Visual-evoked cortical potentials with pattern reversal stimulation were examined in 13 patients and showed bilateral abnormal latencies (Patients 5, 8, and 11–13), were not recordable (Patient 6), or had unilateral abnormalities.
because of low visual acuity (Patients 2 and 9). Normal pattern reversal visual-evoked cortical potentials were found in five patients (Patients 3, 7, and 14–16). Visual-evoked cortical potentials with flash stimulation were found to be present in all examined patients; however, the response was weak in the right eye of Patient 11. Reliable color vision testing and visual field examination were possible in only a limited number of patients because of mental deterioration. Color vision testing disclosed an acquired type II red-green defect of Verriest in two patients (Patients 3 and 13). In Patient 9, color vision was severely disturbed without any typical defect. Goldmann visual field examination was performed in seven patients and was found to be abnormal only in the patient with glaucomatous field loss (Patient 8). At least four patients (Patients 1, 3, 8, and 13) had optic neuropathy, because of pale optic disks, abnormal latencies of visual-evoked potentials, acquired type II color vision defects, or a combination of symptoms.

Aspirated lens material was examined in one patient (Patient 14) and disclosed a cholestanol/cholesterol ratio of 1.71, which was more than five times higher than the ratio of 0.33 that was found in cataractous lens material of a control patient.

**DISCUSSION**

CEREBROTENDINOUS XANTHOMATOSIS IS CLASSICALLY characterized by the following four major features: (1) bilateral cataracts, (2) progressive dysfunction of the central nervous system with mainly pyramidal tract signs and cerebellar ataxia, (3) mental deterioration, and (4) tuberos and Achilles tendon xanthomas. Findings in other studies included peripheral neuropathies, foot deformity, cardiovascular disease or atherosclerosis, history of cholecystectomy because of gallstones, and endocrine abnormalities. In many patients, symptoms begin at about the age of 10 years, but the diagnosis of cerebrotendinous xanthomatosis is made about 20 to 30 years later, sometimes even more than 40 years later. We established a diagnosis of cerebrotendinous xanthomatosis in young patients (Families E and G), because we recognized the association of juvenile cataract and chronic diarrhea as a major clinical feature of cerebrotendinous xanthomatosis in childhood.

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Fig. 2 (Cruysberg and associates). Patient 11. Slit-lamp photograph of the left lens of a child with chronic diarrhea and bilateral cortical cataract, showing multiple line-shaped cortical opacities.

Fig. 3 (Cruysberg and associates). Patient 2. Bilateral anterior polar cataract. Anterior view of left eye (left) after dilation of the pupil. Slit-lamp photograph of left eye (right), showing dense anterior polar cataract and diffuse corticonuclear lens opacity.
The clinical abnormalities are caused by accumulation of cholestanol, the 5α-dihydro derivative of cholesterol, in serum and tissues, including the cataractous lens. The formation of cholestanol results from a block in the metabolic pathway of bile acid synthesis, which is accompanied by the formation of bile alcohols that are normally not detectable in urine. We found that cataract was a symptom at onset in nearly all patients in this series but in only 35% of the cases described elsewhere. We established that the development of this cataract was present in nearly all patients before age 40 years. The cataracts are not congenital but may be diagnosed by age 10 years in nearly half of the patients. Other researchers mentioned the development of cataract in the second decade, the third decade, and the fourth decade. Cataracts may be present without complaints of diminished vision. However, without cataract extraction, visual acuity usually decreases to less than 20/200 before age 40 years. At the age of 50 years, nearly all patients will be aphakic in at least one eye. The type of cataract is mentioned in only half of the cases described before 1975, and they were all zonular. Later, anterior and posterior cortical cataracts, anterior and posterior subcapsular cataracts, coronary cataract, and, as in some of our patients, anterior and posterior polar cataracts, were described. An ultrastructural study showed, especially in the anterior polar region of the lens, numerous vacuoles that were partially disrupted and filled with dispersed granular content, whereas cells in the equatorial region appeared normal. The opacities in the anterior and posterior cortex have been described like a fine cataract, sometimes combined to form small clouds, or rods, with spoke formation in the lenses, blue-white dots, and snowflake-pattern cataracts. The subcapsular opacities appeared as irregular white dots, which sometimes mimicked whorls. The finding that four of our 16 patients initially had anterior polar cataract is remarkable, because this cataract type is considered to be less likely to progress and, therefore, engenders no suspicion of metabolic disease.

Surgical extraction of these cataracts, with or without implantation of intraocular lenses, is associated with a good prognosis for visual recovery. In reported cases, preoperative refraction is for myopia, whereas refraction for aphakia is usually within normal limits. The optic disk may be pale but not atrophic. Visual evoked potentials may be within normal limits, absent because of cataract, or delayed because of optic neuropathy. Visual-evoked potentials showed slow nerve conduction velocities in five of 16 patients in the present study and in two of seven cases in a recent study. If optic nerve dysfunction is established with visual-evoked potentials and color vision tests, then multiple sclerosis may be misdiagnosed in patients with progressive pyramidal tract signs and cerebellar ataxia. Acquired nystagmus, the
result of cerebellar dysfunction in cerebrotendinous xanthomatosis, may further contribute to the misdiagnosis of multiple sclerosis.

Xanthelasma is a planar xanthoma that may affect both eyelids in cerebrotendinous xanthomatosis or may be absent. Palpebral xanthelasma and corneal xanthoma arcus are well known in patients with hypercholesterolemia, however, plasma cholesterol levels are within normal limits in patients with cerebrotendinous xanthomatosis. Other ocular signs are rare and may include unilateral proptosis caused by xanthoma deposition in the extraocular muscles or bilateral exophthalmos in the absence of thyroid dysfunction.

Diagnosis of cerebrotendinous xanthomatosis may be difficult because results of routine examinations of blood, urine, and cerebrospinal fluid are normal. The value of urinary capillary gas chromatography of bile alcohols as a specific test to establish the diagnosis of cerebrotendinous xanthomatosis and to monitor the biochemical effectiveness of the different treatment regimens has been emphasized.

Appropriate biochemical investigations for cerebrotendinous xanthomatosis should be performed in patients with unexplained bilateral juvenile cataracts, especially if these cataracts are associated with any of the following signs: chronic diarrhea since infancy, mental retardation or deterioration, neurologic dysfunction, or xanthomas at any place. Cerebrotendinous xanthomatosis should be excluded if patients who are suspected to have multiple sclerosis develop cataract at a young age. Essentially, cerebrotendinous xanthomatosis should be included in the differential diagnosis of central nervous system disorders associated with cataract.

From the present study, we concluded that the ophthalmologist can play an important role in the early diagnosis of this autosomal recessive disease. Because we have observed that treatment with chenodeoxycholic acid has resulted in a favorable biochemical response in children, we hope that early diagnosis and treatment prevent the devastating central nervous system complications at a later age.

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REFERENCES


