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Presenile Cataract: Consider Cholestanol

Presenile (including juvenile and congenital) cataract is rare. Some cases have a hereditary cause; others result from trauma or chromosomal, endocrine, metabolic, or systemic disorders. Yet, a sizable percentage is of unknown cause. The disorder can occur isolated or more commonly as a part of a generalized systemic condition as well as a part of a syndrome. Genetic determination is likely, especially in the

Figure 4. The right eye of case 3, a 55-year-old woman who experienced endothelial corneal transplant rejection after penetrating keratoplasty for herpetic keratouveitis. A, Biomicroscopic image, obtained 78 days after amniotic membrane (AM) transplantation. Most of the AM patch remains before repeat penetrating keratoplasty but is severely retracted. B, Amniotic membrane is present in the superficial cornea among 3 distinct layers of corneal epithelium (CE) (yellow) (acidic mucopolysaccharide, original magnification ×400). Note the goblet cell (arrow). C, The 3 epithelial layers include original or ingrowing CE cells (1), a squamous epithelial multilayer (2) adjacent to an optically empty space and attached to the AM stroma (AS) with loosely arranged collagen fibers, and a multilayer of squamous CE (3) on top of a translucent cuboid monolayer of AM epithelium (AE) (cytokeratin, original magnification ×200). D, Overview transmission electron microscopic image showing the condensed AS covered anteriorly by a monolayer of partly detached AE and a multilayered CE, and posteriorly by another multilayer of squamous CE. E, Detail of the AE and CE layers on the anterior surface of the AM; the AE is artifically detached from the AS. N indicates nucleus. F, Detail of the interface between the CE and AE showing interdigitating cell processes and desmosomal attachments (arrows) between the epithelial layers. TF indicates tonofilament. G, Detail of the basal aspect of the CE on the posterior surface of the AS showing short segments of basement membrane (large arrows) and small bundles of microfibrils resembling anchoring fibrils (AF) (small arrow). H, Multilayered squamous CE on the posterior surface of the AS showing a discontinuous basement membrane (arrows). I, Multilayered squamous CE on the Bowman layer (BL) of the corneal stroma showing only short segments of basement membrane (arrows).
latter groups. Additional features besides the cataract should indicate the chance of a congenital disorder. Presenile cataract can be sporadic or familial. The mode of its inheritance can be dominant (principally in isolated forms) or recessive (typical in syndromic forms).1

Herein, we describe 2 siblings with early-onset cataract and additional symptoms suggesting the diagnosis of a rare, treatable disorder, cerebrotendinous xanthomatosis (CTX) (Mendelian Inheritance in Man 213700). It is an autosomal recessive lipid storage disease caused by the mutation of the CYP27A1 gene encoding the mitochondrial enzyme 27-sterol hydroxylase. The disorder results from abnormal bile acid synthesis that leads to the production of excessive cholestanol mainly but also of cholesterol to some degree. The accumulation of these sterols in different tissues, particularly in the central nervous system, leads to the varied symptoms of the disease. Traditionally, the diagnosis was based on the presence of presenile cataracts, neurological signs, chronic diarrhea, and tendon xanthomas. However, it has been suggested that the presence of 2 major symptoms (among which cataracts and neurological symptoms are the most common) should already prompt the evaluation to rule out the syndrome in affected patients.2

Indeed, recent reports indicate that the prevalence of CTX is possibly much higher than previously recognized.3

**Report of Cases.** A 31-year-old man (case 1) and his 32-year-old sister (case 2) were born from healthy, nonconsanguineous parents. Both of them had had surgery for presenile bilateral cataracts, which seemed to be the only common feature in their amaness.

**Case 1.** The symptoms of the man began in childhood. His early psychomotor development was delayed. However, he achieved well in school up to age 10 years when his performance deteriorated (currently, his IQ is 91 according to Raven). Persistent, chronic diarrhea; mild ataxia; and hand tremor were present since early childhood and worsened around age 18 years. Yet, results of an extensive neurological workup were normal. He also had a tendency for depression, which resulted in a suicide attempt at age 18 years. His vision began to deteriorate around age 18 years, leading to a surgery for bilateral cataracts at age 29 years. His ataxia began to worsen repeatedly at age 30 years, the reason for which another neurological workup was initiated, including a genetic evaluation.

Cranial magnetic resonance imaging results were normal, and electroencephalography showed diffuse delay. Several genetic test results (karyotype; evaluation for Friedrich ataxia, spinocerebellar ataxias, and fragile X; and mitochondrial mutation panel) were negative. Consecutively, because of the concurrent presence of presenile cataracts, complex neurological symptoms, and chronic diarrhea, the diagnosis of CTX was entertained. Biochemical analyses for serum cholesterol and urinary bile alcohol levels showed marked elevation. The diagnosis of CTX was confirmed by automated sequencing of CYP27A1 that revealed an already published (c.646G>C) and a novel (c.11_20dup) mutation in a compound heterozygous form (Table). This latter mutation causes an early frameshift and consequent amino acid sequence alterations leading to a premature stop at the 175th amino acid position of CYP27A1 (p.Arg8fsX175).

**Case 2.** In light of the brother’s diagnosis, we recommended an evaluation for the sister also, who reportedly had surgery for cataracts at age 20 years and was healthy otherwise. However, on direct questioning, she reported to have had a photovoltaic seizure in the same year. Additionally, she had episodic bouts of diarrhea lasting for a few days every month. She also had surgery for the removal of “lipomas” in the right popliteal region. Her physical examination disclosed no abnormalities except for scaphocephaly, mild exophthalmia, and small subcutaneous nodes in the popliteal region beside the lateral tendons. Neurological examination results were normal. However, electroencephalography showed an irregular baseline pattern and bilateral groups of slow but sharp waves. The biochemical and mutation analyses confirmed her diagnosis of CTX as well (Table).

**Comment.** We present a sibling pair with CTX for whom the key to their diagnosis was the presence of bilateral presenile cataracts. However, it was the existence of additional features such as neurological signs and chronic diarrhea that prompted the biochemical and genetic evaluation for CTX in both patients. Unfortunately, more than 10 years elapsed for both of them following the onset of the cataracts to their definite diagnosis. Yet, specific therapy with chenodeoxycholic acid is available,4 although its clinical efficiency (improvement/delayed progression) can differ from patient to patient. However, the earlier initiated, the better.5 Consequently, we recommend a detailed evaluation for the presence of even mild neurological, gastrointestinal, and dermal (xanthomas) disturbances in each case of presenile cataracts. The concomitant presence of even 1 associated symptom should prompt

| Table. Biochemical and Genetic Evaluation Results for the Cases Presented* |
|---------------------------------------------|---------|---------|------------------|
|                                | Case 1  | Case 2  | Reference Range  |
| Urine bile alcohol level, µmol/L                |         |         |                  |
| Tetrahydroxy form                      | 4.6     | 3.7     | <0.5            |
| Pentahydroxy form                      | 25.7    | 23      | <0.5            |
| Hexahydroxy form                       | 5.5     | 9.7     | <0.5            |
| Serum cholesterol level, arbitrary units/per millimole of creatinine | 157     | 159     | <12.5           |
| CYP27A1 mutation                        | c.11_20dup (p.Arg8fs); c.646G>C (p.Ala216Pro) | c.11_20dup (p.Arg8fs); c.646G>C (p.Ala216Pro) |         |

*The biochemical and genetic analyses were performed as described earlier.6
the evaluation for CTX to support early definitive therapy. Moreover, the measurement of cholesterol levels when a subject is initially seen with presenile cataracts of questionable etiology could be a valuable clinical tool.

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**Familial Retinal Arterial Tortuosity Associated With Tortuosity in Nail Bed Capillaries**

Familial retinal arterial tortuosity (fRAT) is characterized by marked tortuosity of second- and third-order retinal arteries with normal first-order arteries and venous system. Patients have variable transient vision loss owing to retinal hemorrhages after minor stress or trauma. Prognosis is usually excellent. Whether there is systemic involvement is controversial. We report 3 cases of fRAT associated with a high degree of tortuosity of capillaries at nailfold capillaroscopy as an indication of systemic vascular pathology.

**Report of Cases.**

**Case 1.** A woman was first seen at age 19 years because of blurred vision after a minor car accident. Best-corrected visual acuity (BCVA) was 0.9 OD and 0.8 OS. Ophthalmologic examination revealed marked tortuosity of second- and third-order retinal arteries and multiple intraretinal and preretinal hemorrhages in both eyes (Figure 1A). The patient was observed. Four weeks later, BCVA was fully restored in both eyes and the hemorrhages had almost resolved.

Five years later, the patient reported frequent episodes of migraine. Tortuosity of the retinal vessels and BCVA remained unchanged, but the macular reflex appeared duller, and mild thickening of the inner limiting membrane was noted in both eyes (Figure 1B). No hemorrhages were observed.

Seven years after she was first seen, the patient had decreased visual acuity of 0.4 OD and 0.8 OS. She was in her 18th week of pregnancy and had undergone amniocentesis 2 days previously. Fundus examination showed several preretinal, focal hemorrhages in both eyes. Four weeks later, BCVA returned to 1.0 OU and hemorrhages had resolved.

Twelve years after she was first seen, the patient reported episodes of blurred vision once per year, usually following minor exercise. Best-corrected visual acuity had always fully recovered. At this ophthalmologic examination, thickening of the inner limiting membrane was stable and there was 1 asymptomatic preretinal hemorrhage inferotemporal to the macula (Figure 1C). The patient still experienced 5 to 6 episodes of migraine per year but was otherwise healthy.

In visual field tests, scotomas were noted that corresponded to the locations of the hemorrhages. Fluorescein angiography demonstrated no leakage, staining, hypoperfusion, or capillary dropout. Neurologic examinations, including cranial magnetic resonance imaging, yielded normal findings. Extensive examinations in internal medicine, explicitly, tests for serologic factors including virus and bacteria antibody titers and for rheumatologic and autoimmune factors, coagulation tests, and serum electrophoresis, also yielded normal findings. The patient was not taking any systemic medication that would alter coagulation, and blood pressure was within normal limits.

At nailfold capillaroscopy, which was performed at the second and fourth visits, tortuosity of capillaries was highly increased in all fingers of both hands (Figure 1D and E). Minor rarefaction and 1 avascular zone, but no microhemorrhages, were detected. Sodium fluorescein video nailfold capillaroscopy showed normal inflow and outflow, demonstrating absence of capillary spasm; normal transcapillary and interstitial diffusion of fluorescein; and normal halo. No other dermatologic disease, including Raynaud syndrome, was observed.

**Case 2.** The older sister of patient 1 reported a slight decrease in BCVA when first seen at age 28 years. However, BCVA was 1.0 OU. We found marked tortuosity of second- and third-order retinal arteries in both eyes but no hemorrhages. The patient had a history of 1 episode of transient microhematuria of unknown origin, but otherwise reported that she was healthy.

Seven years later, extensive ophthalmologic (Figure 2A), neurologic, and medical examinations were performed, analogous to those in patient 1. All findings were normal with the exception that antinuclear antibodies were 2-fold positive. Findings at dermatologic examination and nailfold capillaroscopy were identical to those in patient 1 (Figure 2B and C).

**Case 3.** The father of patients 1 and 2 was first seen at age 56 years and reported that he had never experienced any visual disturbances. He had a stroke with speech disturbance 8 years earlier, but reported no residual adverse effects. Best-corrected visual acuity was 1.0 OU. Marked tortuosity of second- and third-order retinal arteries was found in both eyes, without hemorrhages.

He was seen 7 years later, and extensive ophthalmologic (Figure 3A), neurologic, and medical examinations revealed atrial fibrillation, and