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Apparently New Syndrome of Sensorineural Hearing Loss, Retinal Pigment Epithelium Lesions, and Discolored Teeth

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We report on a family with early-onset sensorineural hearing loss, abnormal retinal pigment epithelium granularity, accumulation of creamy-white lesions at the level of the retinal pigment epithelium particularly superior to the arcade, and selective discoloration (brown) of molars or canine deciduous teeth that follows an apparent autosomal recessive inheritance pattern. This appears to be a new syndrome that can be distinguished from the known otodental, oculo-acoustic and flecked retina syndromes by the occurrence of distinct dental and ocular abnormalities. Am. J. Med. Genet. 75:13–17, 1998. © 1998 Wiley-Liss, Inc.

KEY WORDS: sensorineural hearing loss; retinal pigment epithelium; discolored enamel; delay in tooth eruption; autosomal recessive

INTRODUCTION

A wide variety of syndromes combining sensorineural hearing loss and eye disease has been observed [Gorlin, 1995]. We report on a family in which 3 of 4 children manifest a previously undescribed combination of oculo-acoustic-dental findings most compatible with autosomal recessive inheritance.

CLINICAL REPORT

Clinical descriptions of each child focus on the audiologic, ocular, and dental findings. The parents are nonconsanguineous, and examinations indicated no dental or ocular abnormalities. All children achieved normal psychomotor development. Fluorescent treponemal antibody, thyroid function, and electrolyte studies were normal. All children had normal hair distribution. No nail pathology was observed. The family was examined twice but was lost to further follow-up before dental photographs or radiographs could be obtained.

The first child (II-1; Fig. 1) was close to 4 years old when his hearing was initially tested. His thresholds sloped from a mild loss at low frequencies to a severe loss at high frequencies (Fig. 2A). Although he experienced some fluctuating conductive overlay to his sensorineural loss, bone conduction thresholds remained stable during the 3 years we were able to monitor this family. CT scan of auditory structures without IV contrast was normal. There was no evidence for temporal bone abnormalities, and the ethmoid air cells were without inflammation bilaterally.

Ocular examination showed small-angle left esotropia that was treated with hyperoptic correction for 1 year. Visual acuity was 20/25 right eye and 20/20 −2 left eye. Pupils reacted normally, anterior segments were normal, and lenses were clear. The fundus showed physiologic color and cupping of the optic nerve head (Fig. 3A,B). The retinal vessel caliber was normal, the foveal reflex was intact and the peripheral retina was flat. However, medium to coarse retinal pigment epithelium (RPE) granularity was present throughout the fundus, particularly in the macula. The fundus was unusual for the creamy-white discrete RPE lesions that were nearly confluent in the superior area just outside the arcade. The appearance and distribution was the same in both eyes. Color vision was normal by Ishihara plates for both eyes. The visual fields on Goldmann perimetry were full to V4e (large) and I4e (small) targets for both eyes, although the left eye showed a relative area of loss to the I4e target between 20 and 40, corresponding to the superior retinal area of white RPE lesions (Fig. 4A). There was no evidence of rod photoreceptor compromise since absolute thresholds after 45 minutes in the dark reached normal rod sensitivity levels at fixation and at 10 and 45 for both eyes. However,

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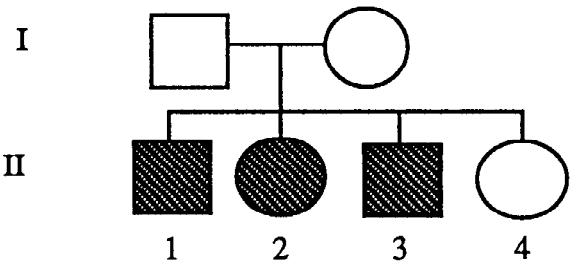

Fig. 1. Pedigree. Shaded family members are affected.

the electroretinogram showed subnormal rod responses of less than 100 μV (where normal is usually greater than 210 μV; Fig. 4B). Cone responses were normal in amplitude but the waveform was remarkable for the absence of negative-going a-wave and an exaggerated triphasic b-wave.

The back molars in both the upper and lower dentitions were brown and slightly smaller than normal, whereas the other teeth were of normal color, shape and size. There was no history of tetracyline ingestion.

The second child, a girl (II-2), was originally diagnosed with bilateral sensorineural hearing loss at approximately 3 years of age with thresholds very similar to those of her older brother (Fig. 2B). This remained stable in the ensuing 3 years.

On ocular examination, she had 20/20 visual acuity for both eyes without correction. The pupils were normally reactive, and anterior segments and lenses were normal. Normal ocular motility was observed. The fundus exam showed normal discs with physiologic color and cupping of the optic nerve head (Fig. 3C,D). The retinal vessels had normal caliber. The peripheral retina was flat. The fovea was intact. The macula showed coarse retinal pigment epithelium granularity and an unusual accumulation of creamy-white lesions at the level of the RPE, particularly superior to the

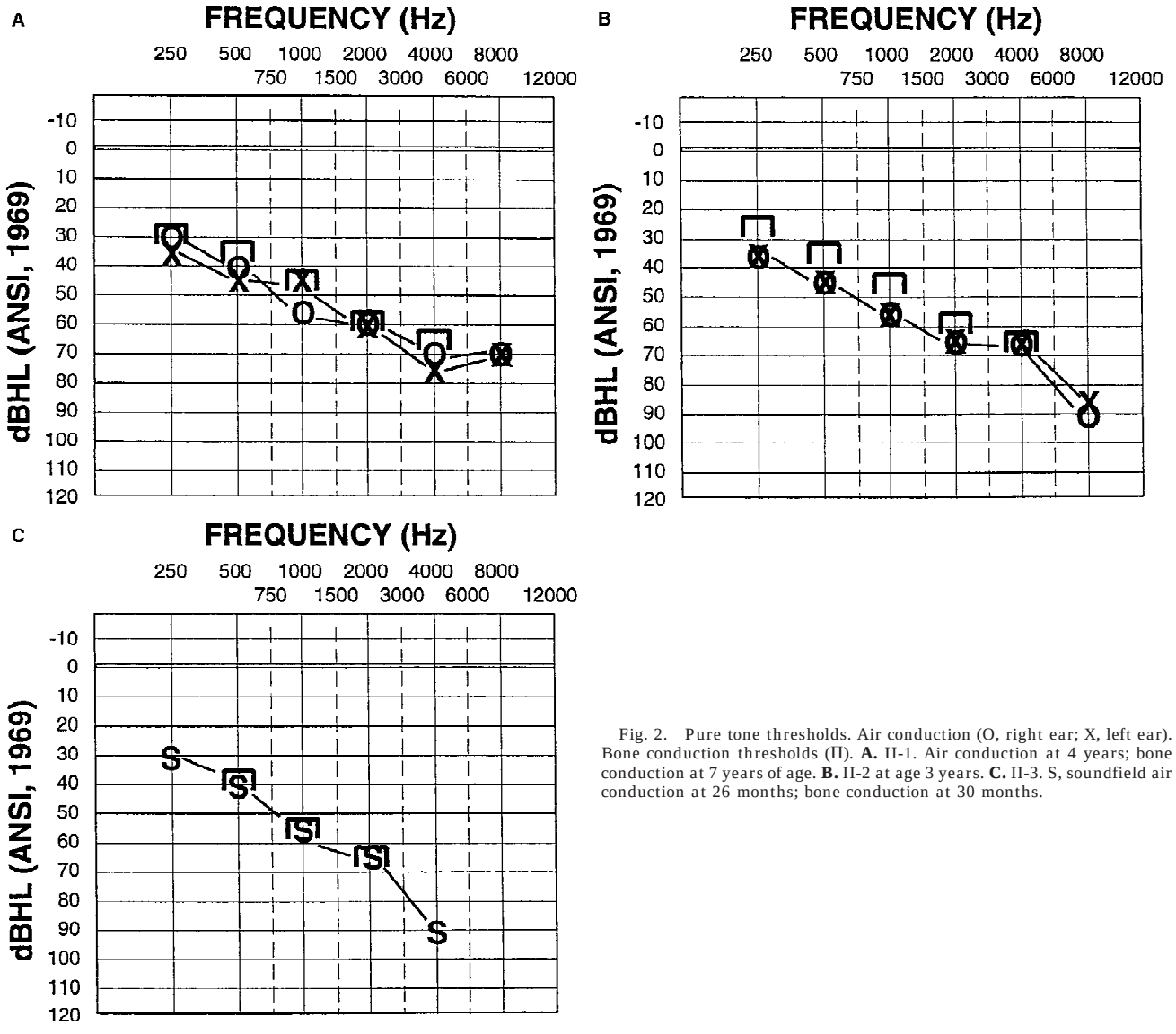

Fig. 2. Pure tone thresholds. Air conduction (O, right ear; X, left ear). Bone conduction thresholds (Π). **A.** II-1. Air conduction at 4 years; bone conduction at 7 years of age. **B.** II-2 at age 3 years. **C.** II-3. S, soundfield air conduction at 26 months; bone conduction at 30 months.

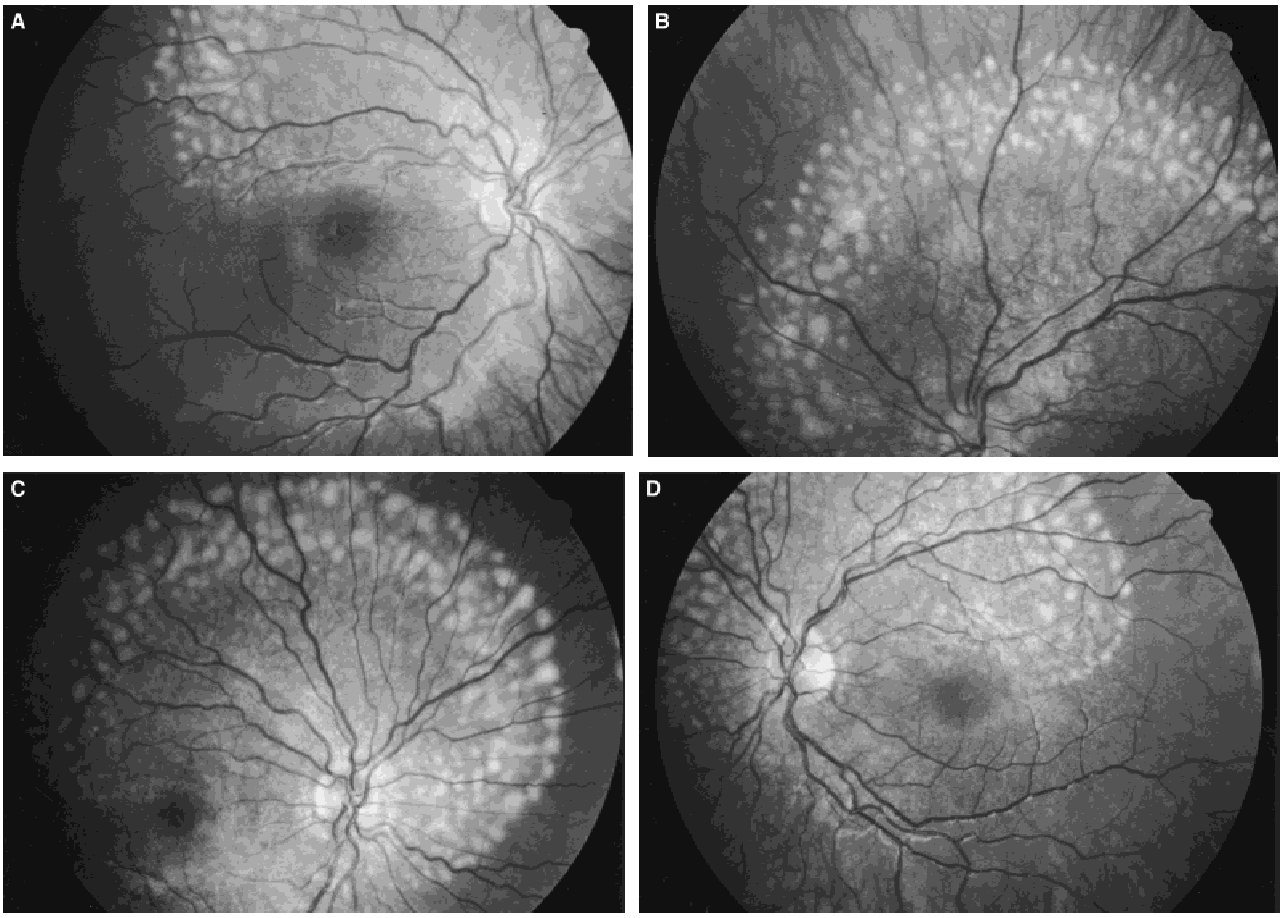

Fig. 3. Ocular fundus photographs show coarse pigmentary retinal changes across the macula, with medium-sized, discrete, creamy yellow-white lesions at the level of the RPE along the superior macula and extending nasal around the nervehead in both eyes (**A,** right; **B,** left) of 6-year-old male (II-1) and his 5-year-old sister (II-2; **C,** right; **D,** left). The pigmentary changes extend into the periphery of all four eyes, but the fovea appears developed, and the optic nervehead and retinal blood vessels are normal.

arcade. The appearance and distribution was the same in both eyes and remarkably similar to her brother (II-1). Color vision was intact, and dark-adapted rod sensitivity was normal.

Examination of the mouth revealed brown molars of normal size and normally-colored canine teeth.

The third child (II-3) was seen for auditory-evoked potential threshold testing at age 2 months and normal thresholds were obtained bilaterally to click and 1,000 Hz tone pip stimuli. At 5 months, behavior responses to sound were normal for age, and ipsilateral acoustic reflex thresholds were normal. He did not return for follow-up until 26 months when behavior threshold testing demonstrated severe sensorineural hearing loss (Fig. 2C). Thresholds were stable at 30 months after which the family was lost to follow-up.

Ocular examination at age 2 demonstrated the ability to fix and follow. Motility was normal. The anterior segments and lenses were clear. Tactile sensation was normal. The funduscopic exam revealed normal physiologic color and cupping. The retinal vessel caliber was normal. The foveal reflex was intact, but the macula showed an abnormal, heavy RPE granularity throughout. Neither eye had developed the creamy-white lesions which were present in the older two sibs.

His deciduous teeth appeared at approximately 11 months with the upper incisors erupting first. Subsequently, he had late eruption of the upper canines and these were small. The lower canines were brown and apparently normal in size. The back molars were all normal in color.

The fourth child, a girl, was seen at 1 month and found to have normal auditory-evoked potential thresholds for click and tone pip stimuli bilaterally. Transient otoacoustic emissions also were normal. On the last examination at 3 months of age, click thresholds were unchanged. Eye examination was not performed.

DISCUSSION

This family exhibits a distinct combination of ocular, auditory, and dental abnormalities. The funduscopic changes consist of an abnormal, coarse retinal pigment epithelium granularity and the accumulation of creamy-white lesions at the level of the retinal pigment epithelium particularly superior to the macular arcade vessels and extending nasally around the nerve head. These specific ocular manifestations are not associated with any of the Usher syndromes which are character-

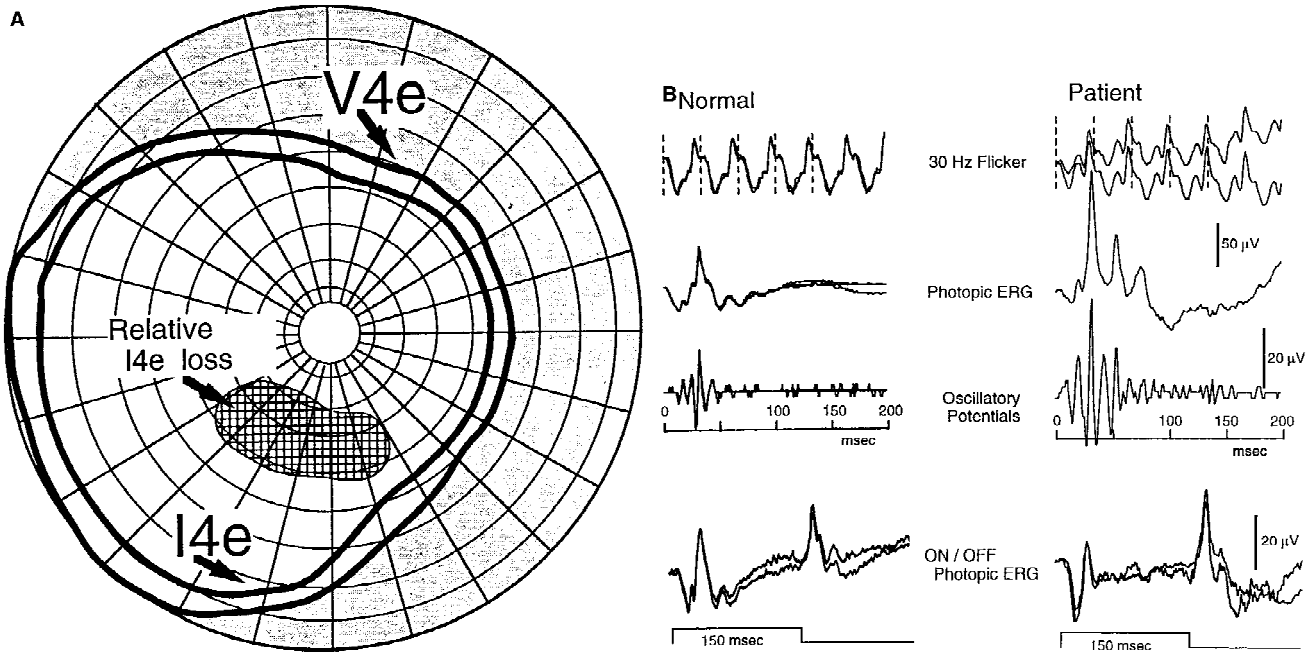

Fig. 4. **A:** Visual field of left eye of 6-year-old II-1 male shows normal peripheral extent with large (V4e) and small (I4e) targets on Goldmann perimeter. Inferior midperipheral relative sensitivity loss corresponds to RPE-level lesions along superior macular arcade in this eye. **B:** Electroretinogram shows dark-adapted rod and light-adapted cone responses of 6-year-old male II-1. Rod responses amplitudes are subnormal at 120 μV (normal >210 μV) but have normal waveform. Cone responses have normal amplitudes, but the waveforms are highly unusual in lacking the initial negative a-wave deflection.

ized by congenital sensorineural hearing loss, vestibular abnormalities and retinitis pigmentosa. The onset of the sensorineural hearing loss in this family occurs during the first 2–4 years of life; whether or not the hearing loss progresses would require long-term follow-up. Normal psychomotor development was achieved by all children, providing further evidence for distinctiveness of this syndrome. The creamy-white retinal lesions appear to occur after age 2 since they were absent in child II-3 at age 2 but present in child II-1 at age 4 and in child II-2 at age 3. Retinal involvement is demonstrated by subnormal rod ERG responses and by a relative inferior visual field deficit which corresponds to the superior retinal area that is most involved. We think these changes may herald a progressive, degenerative retinal process but this would require additional follow-up to establish. The dental abnormalities described in this family consist of late eruption with selective brown discoloration of the canines or molars. Some of the discolored teeth appeared small. No incisor discoloration was observed. The occurrence of sensorineural hearing loss, ocular changes and dental findings in these three children and not in their parents is most compatible with autosomal recessive inheritance.

The observation of a similar-appearing retina should prompt one to consider in the differential diagnosis the so-called "flecked retina" syndromes such as: fundus albipunctatus, retinitis punctata albescens, familial drusen, vitamin A retinopathy, primary hyperoxaluria, secondary oxalosis, Leber's congenital amaurosis, fundus flavimaculatus, Hallervorden-Spatz disease, flecked retina of Kandori, Kjellin's syndrome, and tamoxifen retinopathy [Spencer, 1996]. However, in our case the fundus appearance of an arcuate accumulation of medium-sized, discrete, creamy yellow-white lesions at the level of the RPE is most unusual in ocular syndromes. One of the few in which similar changes occur is Sorsby fundus dystrophy (Fig. 5) which can show RPE-level lesions that are remarkably similar in appearance and distribution to those in our present family [Sieving et al., 1996]. The pathology in Sorsby dystrophy is progressive and leads to central vision loss from vascular ingrowth and subretinal hemorrhage. However, unlike our young affected patients, the lesions in Sorsby dystrophy appear in middle age and inheritance is autosomal dominant. TIMP-3 gene mutations have been described in patients with Sorsby dystrophy that lead to accumulation of debris on or near Bruch's membrane at the level of the RPE [Weber et al., 1994]. Extracellular matrix metalloproteinases are active during development and could be implicated in these young eyes. This suggests that attention to the extracellular matrix protein genes [Apte et al., 1994] may be warranted in this disorder.

Several disorders combining ocular and acoustic abnormalities have been described [Gorlin, 1995]. Among these, Bateman et al. [1980] described a number of patients with retinal degeneration combined with hearing impairment. Our family appears dissimilar from those cases. Patient 7 was a 15-year-old boy with marked visual acuity impairment, a few nuclear opacities in the lens, a moderately pale optic nerve head, arteriolar narrowing, bone spicule formation at the midperiphery, and a macula with minimal pigmentary alterations. This patient also had enamel dysplasia, delayed eruption, congenital absence of the lower sec-

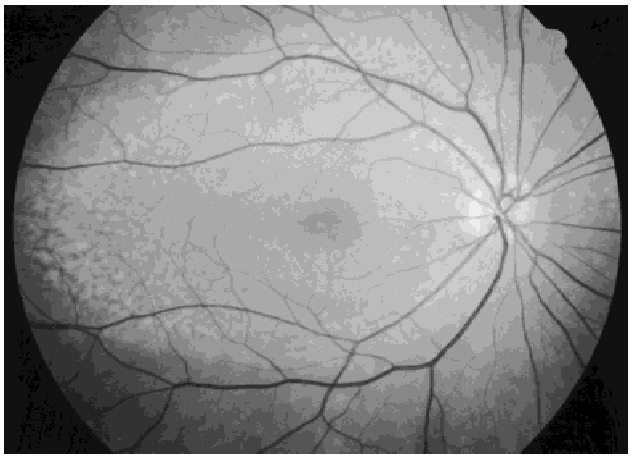

Fig. 5. A 37-year-old woman in a family with Sorsby fundus dystrophy from a ser-181-cys TIMP-3 gene mutation [Sieving et al., 1996] shows fundus changes in both eyes similar to those of our young patients, with creamy yellow-white lesions at the level of the RPE in arcuate distribution superior and inferior to the macula arcade. Her right eye is shown here.

ond premolars, only four permanent posterior teeth, and absent ERG responses. He had apparently normal dark adaptation in that he denied nyctalopia. Interestingly, this individual had minimal pigment granularity of the macula and his hearing loss was diagnosed before he was 2 years old and was stable thereafter. Patient 13 in that report had a stable nonexudative maculopathy without flecks. There was generalized dropout of the pigment epithelium with prominent choroidal vascularity. The retinal periphery showed minimal pigment granularity and the ERG was minimally altered. Hearing loss was moderate to severe and sensorineural. The enamel of the teeth was dark brown, irregular and, on selected teeth, "hard." While the manifestations of these latter two patients affect similar organ systems, we do not think that they describe those observed in the family in this report.

The otodental syndrome is characterized by autosomal dominant inheritance, dental changes, bilateral high-tone sensorineural hearing loss, and normal vestibular testing [Levin and Jorgenson, 1992; Levin et al., 1975]. Usually, the incisors of both dentitions are spared. The crowns of the canine and posterior teeth are enlarged, bulbous and malformed with multiple prominent lobules. An enamel defect is frequently noted on the facial surface of the canine teeth. There is often delayed eruption of the deciduous teeth. Progressive sensorineural hearing loss to about 65 dB is found in all frequencies but is more pronounced at 1,000 Hz. This usually plateaus by the fourth decade. The age of onset of the hearing loss in the otodental syndrome ranges from early childhood to middle age. Retinal lesions have not been described in the otodental syndrome.

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