The Alström syndrome: ophthalmic histopathology and retinal ultrastructure

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SUMMARY A case of pigmentary retinal degeneration causing blindness in early childhood, progressive neurosensory hearing loss, diabetes mellitus, acanthosis nigricans, hypogonadism with normal secondary sex characteristics, and kyphoscoliosis without polydactyly and with no mental retardation is reported. The results of endocrinological studies, karyotype analysis, and digital dermatoglyphics supported the clinical diagnosis of the Alström syndrome. The patient had small globes, bilateral posterior subcapsular cataracts, lacy vacuolation of the iris, ciliary process hyalinisation, unilateral asteroid hyalosis, total absence of rods and cones, intraretinal melanin pigment, retinal pigment epithelium atrophy, focal chorioretinal fusion, preretinal fibrosis, bilateral giant optic disc drusen, and optic nerve atrophy. Electron microscopy of the retina demonstrated large numbers of melanolysosomes, numerous folds of basement membrane material, disruption of Bruch's membrane, and numerous bundles of extracellular collagen fibrils in the retinal pigment epithelium.

In 1959 a syndrome characterised by atypical retinal degeneration, obesity, diabetes mellitus, and neurogenous deafness was described in Sweden.¹ Commonly known as the Alström syndrome, it is believed to be the manifestation of a recessive mutation in a single gene locus. The clinical manifestations, endocrinological profile, and genetic analysis led Alström and colleagues to distinguish this syndrome from the Laurence-Moon and Bardet-Biedl syndromes.

We believe 14 cases of the Alström syndrome have been reported.¹⁻⁷ Goldstein and Fialkow⁶ have analysed 10 definite cases and have identified the cardinal features as: childhood blindness due to pigmentary retinal degeneration, infantile obesity, progressive nerve deafness, diabetes mellitus, and slowly progressive chronic nephropathy. Other features are acanthosis nigricans, baldness, hyperuricaemia, hypertriglyceridaemia, kyphoscoliosis, hyperostosis frontalis interna, and, in males, primary hypogonadism with normal secondary sexual characteristics.

There have been several histopathological descriptions in a variety of secondary retinitis pigmentosa syndromes. In particular, Bisland's report of necropsy

findings in a case of the Laurence-Moon syndrome included ocular histopathology.⁸ The following is the first complete description of the histopathological and retinal ultrastructural findings in both eyes of a man with the Alström syndrome.

Case report

CLINICAL HISTORY

The patient is a 32-year-old white man who at the age of 11 months was noted to have nystagmus OU. He had short stature and relative infantile obesity as evidenced by weight in the 50-75th percentile, while height was less than the third percentile as noted on three occasions over a four-year period (Fig. 1). There was no family history of consanguinity of similar ocular or systemic disorders.

He was first seen at the Massachusetts Eye and Ear Infirmary at the age of 8. Visual acuity was 6/200 OD (+9.50 -1.50 × 180) and 10/200 OS (+11.00 -1.50 × 180). At age 11 visual acuity was CF 1' OU. The globes appeared small, and searching nystagmus was noted. This constellation of findings has been non-specifically termed Leber's amaurosis congenita. However, funduscopy examination revealed vitreous opacities, bilateral pale optic discs with giant drusen,

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Fig. 1 Physical appearance of patient with the Alström syndrome at ages 6 and 28.

and diffuse, black chorioretinal pigment clumps bilaterally. The arteries were sheathed and narrow. An ERG showed no response OU.

Over the next several years visual acuity declined to light perception OU. Posterior subcapsular cataracts formed OU. By the age of 18 he had a mild, high-frequency neurosensory loss, which progressed. Diabetes mellitus was diagnosed at age 20. Acanthosis nigricans was detected at age 23. Evaluation for hypogonadism, first noted at age 27, revealed a penis of normal size with extremely small testes, normal secondary sex characteristics, 46 XY karyotype, normal pituitary responsiveness, and normal digital dermatoglyphics. Marked kyphoscoliosis was noted at this time. Mental retardation, which was suspected at age 8 on the basis of an IQ of 63, was later considered to be minimal, if present at all. At no time was there evidence of polydactyly. During his later years the patient became severely alcoholic and developed, hepatosplenomegaly, oesophageal varices, and upper gastrointestinal bleeding necessitating a porta-caval shunt procedure. His death at age 32 was attributed to chronic alcoholism and acute bronchopneumonia.

NECROPSY FINDINGS

The body weighed 95 kg and was 176 cm in length. The skin showed acanthosis nigricans and was deeply jaundiced. Acute and organising bronchopneumonia were present. There was micronodular hepatic cirrhosis with splenomegaly, splenic infarcts, and oesophageal varices. The pancreas showed islet hyalinisation. There was testicular atrophy with

tubular hyalinisation and no spermatogenesis. The kidneys contained focal glomerular hyalinisation and interstitial fibrosis.

The eyes were 20 mm OD and 21 mm OS in vertical, 21 mm in horizontal, and 20 mm in anteroposterior dimensions. The corneas were 11 mm in horizontal diameters. The external examination, cornea, anterior chamber, iris, ciliary body, and angles were unremarkable in each eye. Posterior subcapsular cataracts were present OU. The vitreous OS had asteroid hyalosis (Fig. 2). The retina had 'bone

Fig. 2 Gross appearance of OS cut in the horizontal plane. The cataract (large arrow) and asteroid hyalosis (small arrows) can be seen.

Fig. 3A Histopathology of the retina. Inner retina with a preretinal membrane (small arrows), vacuolar degeneration (asterisk), and pigment clumping (large arrow). (PAS, $\times 62$).

spicule' pigmentation that spared the macula OU. The choroid was unremarkable. The optic nerve of each eye had giant drusen located at the disc.

Microscopically the uvea, anterior chamber, and angle were unremarkable. There was lacy vacuolation of the iris pigment epithelium and hyalinisation of the ciliary processes. The lens had posterior migration of epithelial cells and bladder cell formation in the posterior subcapsular region OU. The vitreous contained central asteroid hyalosis OS.

There was evidence of preretinal fibrosis OD (Fig. 3A). The retina had markedly hypocellular ganglion cell, inner, and outer nuclear cell layers. Rod and cone outer segments were absent (Fig. 3B). Clumps

of pigment-laden cells were present in the retina (Fig. 3A). Dense PAS-positive hyaline-like material could be seen surrounding these cells. The retinal pigment epithelium (RPE) was disrupted throughout. At certain points Bruch's membrane was thinned, and areas of chorioretinal scarring were present (Fig. 3C). There was optic nerve atrophy OU and giant drusen of the discs (Fig. 4).

ELECTRON MICROSCOPY

Ultrastructural examination of the retina and retinal pigment epithelium was performed. The rods and cones had either degenerated or were absent and most of the outer and inner nuclear layers were

Fig. 3B Absence of rods and cones (asterisks) and RPE degeneration (small arrows), (PAS, $\times 62$).

Fig. 3C Choriocapillaris (CC), an attenuated Bruch's membrane (small arrows), and the absence of RPE cells at a focus of chorioretinal fusion (large arrows). (PAS, $\times 62$).

swollen and disrupted. In the macular region large numbers of melanolysosomes and occasional phagosomes were found.

Clusters of pigment-laden cells, large free pigment granules, and numerous folds of basement membrane material were seen in the inner retina. Bruch's membrane and the basement membrane of the pigment epithelium were found disrupted (Fig. 5). Proliferations of basement membrane material were seen throughout the extracellular space of the pigment epithelial cells (Fig. 5).

Numerous bundles and strands of fine collagenous fibrils were found in the extracellular space throughout the pigment epithelium and among cytoplasmic material from disrupted plasma membranes (Figs. 5, 6A). These fibrils had a diameter of 26–27 nm, which is the same size as the fibrils found within Bruch's membrane (Fig. 6B).

Discussion

The Alström syndrome is a rare autosomal recessive disorder with divergent phenotypic expression. There are a number of other syndromes with similar features. Alport's syndrome includes chronic nephropathy, deafness, cataracts, hyaline bodies of the disc, and retinal degeneration.⁹ However, the cataracts are usually anterior polar, secondary to anterior lenticonus, and the retinal degeneration is more like a fundus albipunctatus than RP.¹⁰ Osteopetrosis features nystagmus, optic atrophy, and neurogenic deafness, all due to a primary disorder of bone.¹¹ This is much less similar to the Alström syndrome than is Cockayne's syndrome, where pigmentary retinal degeneration, cataracts, nystagmus,

band keratopathy, and deafness are present.¹² A strong similarity between the Alström syndrome and the Laurence-Moon and Bardet-Biedl syndromes has prompted some clinicians to consider the Alström syndrome to be a variant of these.^{3,13} While pigmentary retinal degeneration and obesity are present in 90–100% of cases in all these syndromes, Alström's can be distinguished from the others by the presence of nerve deafness (100% in Alström's, 5% in Bardet-Biedl), diabetes mellitus (90% in Alström's, 4% in Bardet-Biedl) and the relative absence of mental retardation (95% in Bardet-Biedl) and digital anomalies (75–80% in Bardet-Biedl).^{6,14} Furthermore, the onset of profound blindness occurs at a much younger age in patients with the Alström syndrome.^{3,6} The similar features of these disorders and others, particularly Edwards's syndrome,¹⁵ suggests that all these may be variable expressions of the same disease. However, as suggested by Schachat

Fig. 4 Giant drusen of the optic disc. (PAS, $\times 9$).

Table 1 Summary of 13 cases of the Alström syndrome

Feature	No.	%
Posterior subcapsular cataracts	13	100
Pigmentary degeneration of retina	11 observed 2 presumed*	100
Optic disc pallor	7	50
Narrow retinal arteries	5	38
Asteroid hyalosis	2	15
Optic disc drusen	1	7

* Advanced cataracts precluded fundus examination in two cases.

and Maumenee,¹⁴ there is value in attempting to separate these disorders into subgroups.

The presence of pigmentary retinal degeneration causing blindness at a very early age, progressive neurosensory hearing loss, insulin-dependent diabetes mellitus, acanthosis nigricans, hypogonadism with normal secondary sex characteristics, kyphoscoliosis, and the absence of polydactyly and mental retardation lead us to conclude that this is a case of the Alström syndrome.

Table 1 summarises the eye findings in this case and

12 cases of the Alström syndrome that were adequately described in the literature. Posterior subcapsular cataracts (PSC) were present in all cases. This is substantially greater than the 41% of 291 cases of various forms of hereditary retinal degenerations found to have PSC by Heckenlively.¹⁶ A fair comparison is limited by the small number of Alström cases and the heterogeneity of the larger group. It is interesting to note, however, that when Pruett examined 116 eyes of 58 patients with primary retinitis pigmentosa the prevalence of PSC was 50%.¹⁷ Furthermore, in a review of 215 cases of Bardet-Biedl syndrome only 3% were found to have cataracts.¹⁴ The presence of diabetes mellitus in patients with the Alström syndrome may account for the high prevalence of PSCs in this condition.

The pathological findings in this case consist of small globes with posterior subcapsular cataracts, lacy vacuolation of the iris, ciliary process hyalinisation, asteroid hyalosis, pigmentary retinal degeneration, RPE atrophy, focal chorioretinal fusion, preretinal fibrosis, giant optic disc drusen, and optic nerve atrophy.

Fig. 5 RPE ultrastructure. Shows a retinal pigment epithelial cell nucleus (N) with basement membrane (BM) proliferation throughout the extracellular space. Bruch's membrane is disrupted (long arrow) and fine collagenous fibrils are present in the extracellular space (short arrows). ($\times 9800$).

The iris and ciliary process changes are commonly seen in diabetics. A characteristic vitreous degeneration paralleling the degree of visual field loss in retinitis pigmentosa was described by Pruett.¹⁷ In his study vitreous opacities consisted of translucent round or oval aggregates that were evenly suspended throughout the gel. In another study¹⁸ of 42 eyes with retinitis pigmentosa 90.5% had spindle-shaped and/or cottonball-like opacities in the posterior vitreous. Minute round or oval whitish granules were evenly distributed throughout the vitreous in 78.5% of these cases. Campo and Aaberg have suggested that such vitreous opacities may result from the vascular incompetence they demonstrated in four patients with the Bardet-Biedl syndrome.¹⁹ Asteroid hyalosis was not described in any of these studies. It is not clear whether this finding is incidental or whether it represents a further manifestation of vitreoretinal degeneration in this disease. The unilaterality in our case would seem to support the former. However, the presence of asteroid hyalosis in at least one other case of the Alström syndrome (bilateral) and perhaps a third case (Table 1) suggests that this abnormality

may be more frequent in this condition than other secondary pigmentary retinal degenerations.

The pigment cells containing melanolysosomes and the bone spicule pigmentation found around blood vessels have been previously reported,²⁰⁻²² and are believed to be related to the advanced stages of the disease.²³ It is not known whether the migration of pigment cells found in the retina are macrophages or migrated retinal pigment epithelium. However, the proliferation of basement membrane among the pigment cells in these areas suggests that they may be derived from the RPE.

The presence of fine collagenous fibrils in the extracellular space was a prominent ultrastructural finding. Although no fibroblasts were seen in these regions, similar findings have been seen in other cases in association with fibroblast proliferation (Szamier RB, personal communication). It is believed that such fibroblasts arise from the choroid and gain access to the retina via breaks in Bruch's membrane. An alternative explanation for the origin of the collagen fibrils is that they may have been synthesised by dysplastic RPE cells.

Fig. 6A Extracellular ultrastructure. The RPE with bundles of collagenous fibrils (arrow) at the apical portion of a cell. A nucleus (N), located in what appears as a second layer of RPE cells probably results from RPE proliferation. ($\times 1380$).

Fig. 6B Demonstrates fibrils in Fig. 6A, which measured approximately 26–28 nm. ($\times 33\,655$).

The findings in this case differ from the histopathological characteristics of primary retinitis pigmentosa in that foci of chorioretinal fusion and optic nerve atrophy are not commonly seen in primary retinitis pigmentosa.²⁴ Although optic disc drusen have been previously reported in RP, these are usually parapapillary and are not elevated as in the case above.²⁵ The histopathological features of the Alström syndrome do resemble those found in other secondary or pseudoretinitis pigmentosa syndromes.^{8,22,24} Indeed, it would seem that on the basis of the ocular histopathological findings alone these syndromes cannot be distinguished.

This project was carried out at the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

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