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Rare disease

Alström syndrome – an uncommon cause of early childhood retinal dystrophy

Leo Sheck,[1] Rasha Al-Taie,[2] Dianne Sharp,[2] Andrea Vincent[1]

[1]Ophthalmology Department, University of Auckland, Auckland, New Zealand;
[2]Ophthalmology Department, Auckland District Health Board, Auckland, New Zealand

Correspondence to Dr Leo Sheck, l.sheck@auckland.ac.nz

Summary

Alström syndrome (AS) is a ciliopathy and an uncommon cause of syndromic retinal dystrophy. This case reports findings in a 5-year-old boy with severe early onset retinal dystrophy, and how the recognition of extraocular features with genetic analysis led to the correct diagnosis of AS after 4 years of investigation.

BACKGROUND

Alström syndrome (AS) is an autosomal recessive condition with a prevalence of 1:1000000.[1] The diagnosis of AS retinal dystrophy is difficult for ophthalmologists because of its rarity and the unfamiliarity with its associated extraocular features. However, in patients with AS and other syndromic retinal dystrophies, the ophthalmologist may save lives by appropriate referrals to cardiology, endocrinology and other medical specialties. This case elegantly illustrates the importance of a complete physical and ocular examination, in conjunction with electrophysiology and genetic testing, in the diagnosis of rare syndromic retinal dystrophies. Furthermore, the clinical findings of this patient demonstrated the phenotypic overlap in different ciliopathies, including AS, Bardet-Biedl syndrome (BBS) and Leber congenital amaurosis (LCA).

CASE PRESENTATION

A 5-year-old boy was referred to the Auckland Ocular Genetics Clinic with poor vision. Nystagmus was observed at 3 months of age. At 1 year of age, hypermetropia was noted and glasses prescribed. Electroretinography (ERG) at 18 months of age, with lid electrodes and Grass strobe flash stimulus, could not identify cone mediated function, with an apparent rod-mediated response. A diagnosis of achromatopsia was made, and red glasses prescribed. Recently he became less confident in dim light and disliked his glasses indoors. A repeat ERG performed at age 5 (lid electrodes/International Society for Clinical Electrophysiology of Vision standard/Ganzfeld stimulus) could not identify rod nor cone mediated function, suggesting a severe rod-cone dystrophy.

Delivered at term following a normal pregnancy, his medical history was unremarkable, with no cardiac history, hearing loss, diabetes, renal dysfunction, or polydactyly. There was no family history of any ocular disorders, and no documented consanguinity.

On examination at age 5: best corrected visual acuity was 6/60 right and left eye oculi uterque (OU), hypermetropia (+6.5 Dioptres OU) and a binocular conjugate jerky horizontal nystagmus of low amplitude and medium frequency was observed. On slit-lamp biomicroscopy examination, the anterior segment was unremarkable. Pupils reacted briskly to light with no relative afferent pupillary defect or paradoxical pupil responses. On fundus examination, he appeared to have mild granularity to the peripheral retina. The optic discs, macula and retinal vessels were normal.

Systemically he was overweight–weight at the 99th percentile and height 90th percentile for his age group, with a mild expressive language developmental delay and small external genitalia. No polydactyly nor skin tags were observed.

INVESTIGATIONS

The most likely diagnosis was felt to be LCA, and genetic testing for LCA used a microarray (v.8.0, Asper Ophthalmics, Estonia) containing 641 sequence variants in 13 LCA genes, but found no mutations. Reassessment of the phenotype, particularly with regard to the obesity and abnormal genitalia, raised the possibility of BBS. Testing with the BBS microarray (Asper Ophthalmics, Estonia, v5.0–312 mutations in genes BBS1 to BBS10, BBS12, PHF6, ALMS1 and GNAS1), demonstrated compound heterozygosity in the ALMS1 gene. The two non-sense mutations were c.8164C>T in exon 10 and c.6305C>A in exon 8 resulting in p.I2102X. Both mutations were previously described as being pathogenic. The c.8164C>T mutation was reported in three siblings of a Turkish family with AS, all with pigmentary retinopathy.[2] The affected individuals were homozygous for this mutation. This mutation was predicted to result in premature truncation of the ALMS1 protein (p.S2722X). The c.6305C>A mutation was reported in a English AS patient with compound heterozygous mutations.[3] It was predicted to result in the premature termination of the ALMS1 protein (p.I2102X).

DIFFERENTIAL DIAGNOSIS

- Alström syndrome
- Bardet-Biedl syndrome
- Leber congenital amaurosis.

Table 1 Differential diagnoses for early onset retinal dystrophies.[10 13] Only the main extraocular features of the syndromic disorders are provided.

Non-syndromic retinal dystrophy	Syndromic retinal dystrophy	Extraocular features
Isolated Leber congenital amaurosis (LCA)	Usher's syndrome	Congenital deafness
Congenital stationary night blindness	Senior-Loken syndrome	Nephronophthisis
Ocular albinism	Saldino-Mainzer syndrome	Renal dysplasia, cerebellar ataxia, skeletal dysplasia
Achromatopsia	Joubert syndrome	Cerebellar vermis hypoplasia, renal abnormalities
	Bardet-Biedl syndrome	Polydactyly, obesity, genitourinary malformation, mental retardation
	Alström syndrome	Obesity, diabetes, acanthosis nigricans and dilated cardiomyopathy
	Abetalipoproteinemia	Celiac syndrome, ataxic neuropathy, acanthocytosis, absent serum beta lipoprotein
	Peroxisomal disorders–infantile refsums disease, neonatal adrenoleukodystrophy and Zellweger disease	Peripheral neuropathy, cerebellar ataxia, hearing loss, developmental delay, craniofacial abnormalities
	Batten disease	Neuronal ceroid lipofuscinoses with developmental delay, seizures, psychoses and dementia

OUTCOME AND FOLLOW-UP

Following the diagnosis of AS, he was referred to a paediatrician and a paediatric cardiologist. Biochemical testings showed normal fasting glucose and renal function, mildly elevated triglycerides and decreased high density lipoprotein. A renal ultrasound was normal. The ECG and echocardiogram were normal with no evidence of hypertrophy. Although this patient appears to have normal hearing, a formal audiology test has been requested.

Ongoing regular follow-ups have been arranged with paediatrics and cardiology services for potential systemic complications in the future.

DISCUSSION

This case illustrates the importance of considering a systemic diagnoses such as AS and BBS in severe early childhood onset retinal dystrophy/LCA. AS is a rare syndrome with only around 450 cases diagnosed worldwide since it was first described 50 years ago.[1] AS commonly presents with visual loss from retinal dystrophy and various degrees of metabolic disturbances, such as diabetes and obesity, in the recently reported cases.[4–7] Before the advent of genetic diagnosis, a case of AS was reported to be misdiagnosed as BBS.[8]

AS and BBS phenotypes overlap considerably, sharing features of autosomal recessive inheritance, retinal dystrophy, obesity, diabetes mellitus and renal failure.[9] Children with AS often develop dilated cardiomyopathy, a common cause of death in infancy.[10] Sensorineural hearing loss affects 50% of AS patients.[9] The abnormal genitalia, polydactyly and neurological impairment, variably present in BBS, are not usually present in AS.[9] The presence of small external genitalia and the absence of hearing loss in this case are atypical for AS.

Genetic characterisation of AS, BBS and LCA (termed 'ciliopathies')[9] has highlighted an underlying similarity in pathogenesis. Almost all vertebral cell types process primary cilia, which play important roles in cellular transport and structural support. The product of the causative AS gene, ALMS1, localises to the ciliary basal body. Mutations in ALMS1 cause defective transport of rhodopsin in photoreceptors, interfering with the cilia maintenance and biogenesis.[9] Fifteen causative BBS genes have been identified (BBS1 to BBS12, MKS1, CEP290, C2ORF86).[11] BBS1 to BBS12 together form the BBSome and the BBS chaperone complex.[12] This BBSome localises to the basal bodies and centromeres of many tissues, including connecting cilium of the photoreceptors, renal tubule cilia and olfactory epithelial cilia.[9] Dysfunction of the photoreceptor (PR) cilium is implicated in LCA. At least four LCA genes encode for cilia functioning (retinitis pigmentosa GTPase regulator interacting protein (RPGR-IP), LCA5, CEP290, TULP),[11] example, RPGR-IP anchors RPGR to the PR connecting cilium required for disc morphogenesis.[9] An underlying ciliary dysfunction explains the similar ocular features in AS, BBS and LCA, and the similar multisystem manifestations in AS and BBS. This case suggests that BBS and AS represent variable manifestations along a phenotypic continuum, with ALMS1 mutations causing a BBS phenotype (abnormal genitalia and neurological impairment).

The differential diagnosis for poor vision and nystagmus in early childhood includes LCA, achromatopsia, congenital stationary night blindness and the systemic retinal phenotypes (table 1).[13]

The correct diagnosis hinges on recognising the atypical extraocular features. This case illustrates the importance of the synergy of detailed clinical and family history, careful ocular and systemic examination, electrophysiology and genetic testing, in the diagnosis of early childhood retinal dystrophy. In addition, the syndromic retinal dystrophies often carry systemic associations that can be life-threatening if undetected (e.g. cardiomyopathy in AS). The ophthalmologist should consider referring patients with suspected syndromic retinal dystrophies to a general physician to detect any systemic pathology. Once the diagnosis of a particular syndromic retinal dystrophy is made, the ophthalmologist should liaise with all relevant specialists (in the case of AS – paediatrician, cardiologist and endocrinologist) regarding the management of potential associated systemic complications.

Genetic testing allows a definitive diagnosis, and may predict visual prognosis as with LCA genotype-phenotype correlations,[10] and allows the clinician to be alerted to systemic complications. Other benefits of genetic testing include informed genetic counselling, prenatal diagnosis and preimplantation diagnosis, with gene-related therapy. The increasing availability and cost-effectiveness of genetic testing allow it to be an integral component of management in the inherited retinal dystrophies.

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Learning points

- In syndromic retinal dystrophies: the synergy of detailed history, careful ocular and systemic examination, electrophysiology and genetic testing is essential in the diagnosis.
- Accurate diagnosis requires knowledge of associated extraocular features (table 1).
- Underlying pathophysiology involving ciliopathy results in overlapping phenotypes.
- Appropriate referral by the ophthalmologist to other specialities can maximise lifespan.

Competing interests None.

Patient consent Obtained.

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