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Alström Syndrome

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1. Introduction

Recent advancements in genetic research that have elucidated the function of some of the rare disease-causing genes have suggested that a large number of genetic disorders with widely divergent phenotypes, that were not previously identified as related, may be, in fact, highly related in cellular function or common pathways. A classic example of this is the recent category of disorders called ciliopathies. Cilia and flagella are ancient, evolutionarily conserved organelles that project from cell surfaces to perform diverse biological roles, including whole-cell locomotion; movement of fluid; chemo-, mechano-, and photosensation; and sexual reproduction. Over the past ten years, several studies demonstrated the connections between cilia, basal bodies and human diseases with a wide phenotypic spectrum, including randomization of body symmetry, obesity, cystic kidney diseases and retinal degeneration. Defects in ciliary structure or function can lead to a broader set of developmental and adult phenotypes, with mutations in ciliary proteins now associated with nephronophthisis, Joubert Syndrome, Meckel-Gruber Syndrome, Bardet-Biedl Syndrome, and Alström Syndrome (ALMS), [Badano et al., 2006]. Further study of these diverse ciliopathies could lead to an understanding of the phenotypic patterns that could potentially have predictive and therapeutic value. Alström Syndrome (ALMS; MIM #203800), first described by Carl-Henry Alström, in 1959 [Alström et al., 1959], is a rare condition that affects many body systems. ALMS is characterized by a constelation of serious or life-threatening medical problems including sensory deficits, obesity, type 2 diabetes mellitus, and multiple organ failure. The signs and symptoms of ALMS vary in severity, and not all affected individuals have all of the characteristic features of the disorder, making the diagnosis more difficult. Additionally, many of the signs and symptoms of this condition begin in infancy or early childhood, although some appear later in life. The major phenotypes usually observed in children with ALMS include cone–rod retinal dystrophy beginning in infancy and leading to juvenile blindness, sensorineural hearing impairment, insulin resistance, and obesity, and congestive heart failure (CHF) due to dilated cardiomyopathy (DCM). As patients reach adolescence, more of the major phenotypes develop, including type 2 diabetes mellitus, hypertriglyceridemia, hypothyroidism, and short adult stature. Males and females have hypogonadism and are infertile. Pulmonary, hepatic, and renal phenotypes are progressive [Marshall et al. 1997,

2005]. The primary cause of mortality among young affected patients is cardiac involvement from dilated cardiomyopathy whereas renal failure is the major cause of death among the older subgroup [Marshall et al., 1997]. Systemic fibrosis is commonly observed [Marshall et al., 2005]. About 700 affected individuals have been identified worldwide. The estimated prevalence is of <1: 5,000,000 [JD.Marshall, Personal communication]. Ethnically or geographically isolated populations have a higher-than-average frequency of Alström syndrome [Deeble et al., 2000 & Ozgül et al., 2007].

2. Diagnosis

2.1 Clinical diagnosis

The diagnosis of ALMS is usually established by clinical findings. Diagnosis may be delayed because some features begin at birth and others emerge as the child develops. Diagnosis can also be difficult due to variable expression of the severity of the clinical features both within and among families. It is important to note that, although some of the features are seen frequently, affected individuals may not have all of the symptoms discussed below.

2.1.1 Major features

Cone-rod dystrophy. The first symptoms are pendular or searching nystagmus and extreme photodysphoria or light sensitivity. The retinal dystrophy in ALMS often develops within a few weeks after birth and virtually all children exhibit low vision within the first year of life [Malm et al., 2008; Russell-Eggitt et al., 1998]. Fundus examination in the first decade may be normal or may show a pale optic disc and narrowing of the retinal vessels. Electroretinography (ERG), required to establish the diagnosis of cone-rod dystrophy, is abnormal from birth, eventually with impairment of both cone and rod function. Rod function is preserved initially but deteriorates as the individual ages. By 9 – 10 years of age, visual acuity is severely impaired. There is increasing constriction of visual fields, leading to total blindness with no light perception by age 16- 20 years [Marshall et al., 2007a, Michaud et al., 1996]. The severity and age of onset of the retinal degeneration vary among ALMS patients [Malm et al., 2008]. Retinal changes include attenuated vessels, pale optic discs, and partial atrophy of the retinal pigment epithelium. Pathological studies show a reduction of cell layers in the posterior retina and depletion of peripheral cells, the outer nuclear layer, and photoreceptors [Sebag et al., 1984, Vingolo et al., 2010]. Exudative retinopathy was described in Alström Syndrome [Gogi et al., 2007]. Vision may be aided in the first few years if the child is given prescription dark, red-tinted glasses. Cataract is a common finding and some patients might transiently benefit from its treatment/removal [Marshall et al., 2005, 2007, Satman et al., 2002].

Progressive bilateral sensorineural hearing impairment

Most patients develop mild-to-moderate bilateral sensorineural hearing loss in early childhood (<10 years) that is slowly progressive, particularly in the high-frequency range [Van den Abeele et al., 2001; Welsh 2007]. There is a high incidence of otitis media and fluid retention along with a high susceptibility to glue ear, which compounds the existing sensorineural impairment [Marshall et al. 2005, Michaud et al., 1997]. Hearing loss may be detected as early as age one year in some patients, although wide differences in acuity exist. Although bilateral hearing aids generally benefit most children, about 10% progress to profound deafness and must rely on tactile signing for communication [Marshall et al.,

2007a]. There is evidence that vestibular function is abnormal in some patients. [Möller, 2005]. Because hearing loss develops gradually and the onset is post-lingual, children typically do not experience the speech problems often associated with deafness. These early changes in neurosensory capabilities can have tremendous impact not only on the social development of the child but also on his/her adaptation to the external environment [Joyet al., 2007, Van den Abeele et al., 2001].

Obesity

Obesity in Alström Syndrome is an early and consistent feature observed in nearly all affected children [Marshall et al., 2005, 2007a]. Body Mass Index (kg/m^2) is typically greater than 25 or >95th centile, with the distribution of adipose tissue predominantly viscerally and subcutaneously [Paisey et al., 2008]. Birth weight is normal, but rapid weight gain usually begins at approximately 6 months to 1 year of age. In some individuals body weight tends to normalize, decreasing into the high-normal to normal range after adolescence. The moderation of weight does not seem to be correlated with the onset of other serious complications such as CHF, T2DM, or renal failure [Minton et al., 2006]. Wide shoulders, a barrel chest, a 'stocky' build, and truncal obesity are typical [Marshall et al., 2007a]. However, both waist circumference and body fat percentage (as measured using dual-energy X-ray absorptiometry) negatively correlated with age, and was independent of Body Mass Index, indicating the possible recruitment of more metabolically active fat stores [Minton et al., 2006]. The presence of hyperphagia has been controversial, although both hyperphagia and food obsession are common anecdotal complaints [Marshall et al., 1997, 2005].

Growth and development

Children grow rapidly and are initially tall for their age with a height >50th centile, with 2–3 years advanced bone age prior to puberty. However, early closure of the growth plates results in height below the 50th centile by age 14–16 years [Michaud et al., 1996]. Thoracic and lumbar scoliosis and kyphosis commonly develop in the early teenage years and can progress rapidly. Many patients have a 'buffalo hump' of increased fatty tissue above the shoulders [Marshall et al., 2005, 2007a]. Abnormalities of the insulin-like growth factor system (IGFs) of affected patients have been demonstrated [Maffei et al., 2007, Mihai et al., 2008, 2009]. Yet, the exact reasons for short stature remain to be determined.

Dilated cardiomyopathy

DCM can occur at any age, but is seen most typically during infancy. Onset, progression, and clinical outcome of the DCM vary, even within families [Hoffman et al., 2005, Makaryus et al., 2003]. Approximately 40% of affected infants have a transient but severe DCM with onset between age three weeks and four months [Marshall et al., 2005, Worthley & Zeitz, 2001]. Most of these children survive and make an apparently full recovery in infancy. The proportion of those with ALMS who develop infantile-onset DCM may be underestimated because some infants who succumb early may have undiagnosed Alström syndrome.

A subset of 10-15% of patients does not experience infantile DCM, but develop cardiomyopathy for the first time as adolescents or adults. These patients present with a progressive restrictive cardiomyopathy [Worthley & Zeitz, 2001], identified between the teens to late 30s. Although DCM is the most common underlying cause of death in the infantile period, survival for children with infantile-onset tends to be better than that for

adult-onset. Marshall et al showed that while one-third of adult-onset DCM patients died, ~74% of infantile-onset DCM patients survived [Marshall et al., 2005]. As these children grow older, their cardiac function tends to be low-normal, and they remain at risk for a recurrence of CHF as adolescents or adults, with a poor prognosis. Postmortem myocardial fibrosis has been described [Minton et al., 2006]. Cardiac magnetic resonance imaging suggests myocardial fibrosis may be present both in clinically affected and asymptomatic individuals [Loudon et al., 2009].

Augmented aortic systolic pressure may also contribute to heart failure [Smith et al., 2007].

DCM in infants in the presence of nystagmus and photophobia should be a strong indicator of a diagnosis of ALMS.

Pulmonary disease

Chronic respiratory illness is one of the most frequent complaints and ranges in severity from frequent bronchial infections to chronic asthma, sinusitis/bronchitis, alveolar hypoventilation, and frequent episodes of pneumonia. The chronically inflamed airways are hyper-reactive and highly sensitive to triggering or irritating factors. In some patients, as inflammation continues, the lungs are infiltrated by fibrotic lesions and moderate to severe interstitial fibrosis has been reported [Marshall et al., 2005]. Pulmonary disease can be quite severe and include chronic obstructive pulmonary disease and pulmonary hypertension, secondary to pulmonary fibrosis. Respiratory infections with sudden reduced blood oxygen saturation have triggered sudden death. Acute hypoxia and acute respiratory distress syndrome in some older patients probably results from a combination of pulmonary fibrosis and severe scoliosis [Khoo et al., 2009; Florentzson et al., 2010].

Insulin resistance/type 2 diabetes mellitus

Two of the earliest metabolic changes in ALMS, insulin resistance and hyperinsulinemia, have been observed in patients as young as 1 year of age, sometimes before the onset of obesity [Marshall et al., 2005, 2007a]. Most children will eventually develop T2DM, some as early as age 4, but there is wide variability in the age of onset. The median age of onset is 16 years. T2DM in Alström syndrome is the result of tissue resistance to the actions of insulin, as demonstrated by an elevated plasma insulin concentration and glucose intolerance that usually present in childhood [Marshall et al., 2005, 2007a]. *Acanthosis nigricans,* a common feature in ALMS, consistent with severe insulin resistance, obesity, hyperinsulinemia, is described in about one-third of patients, whether or not they have diabetes [Marshall et al., 2005, 2007a]. However, in a small study of 12 unrelated individuals with ALMS, severe childhood obesity, BMI and waist circumference decreased with age, whereas insulin resistance increased [Minton et al., 2006]. Interestingly, ALMS patients with T2DM do not appear to develop typical peripheral sensory neuropathy symptoms and maintain good protective sensation despite comparable hyperglycemia and dyslipidemia seen in other types of diabetes. This suggests the *ALMS1* mutations might in some way protect against hyperglycemia-induced sensory neuropathy [Paisey et al., 2009]. However, studies of nerve conduction in these patients are needed to confirm these findings.

Hepatic disease

Nearly all patients with ALMS may have some degree of liver involvement that first presents with fatty liver. Initially, overt clinical manifestations are absent, but transaminases and gamma-glutamyl transpeptidase could be elevated. Ultrasound may show evidence of

steatosis, steatohepatitis, and enlarged liver and spleen, which can progress in ALMS patients as they grow older. In some individuals, hepatic inflammation and fibrosis develops, with a highly variable age of onset, clinical course, and prognosis. As the disease progresses, liver function tests are further disturbed with altered prothrombin values or elevated International normalized ratio (INR) and ammonia. Progression to hepatic failure can occur in childhood [Quiros-Tejeira et al., 2001], but usually worsens in the second to third decades. Portal hypertension, hepatosplenomegaly, cirrhosis, esophageal varices, ascites, and liver failure are among the late clinical signs and the upper gastro-intestinal hemorrhage due to portal hypertension is a cause of death in some patients [Marshall et al., 2005, 2007a]. It is not yet known why the hepatic function becomes serious in some children, while others remain stable [Awazu et al., 1995, 1997, Connolly et al., 1991 & Marshall et al., 2005].

Liver biopsies and postmortem examination have revealed varying degrees of steatohepatitis, hepatic fibrosis, cirrhosis, chronic nonspecific active hepatitis with lymphocytic infiltration, patchy necrosis, [Marshall et al., 2005, Quiros-Tejeira et al., 2001]. Macrovesicular steatosis can be present or absent [Marshall et al., 2005]. Other gastrointestinal manifestations include upper gastrointestinal pain, chronic diarrhea, constipation, cecal volvulus, and gastroesophageal reflux [Marshall et al., 2005; Khoo et al., 2009].

Renal disease

The age of onset, progression rate, and severity of renal involvement are variable in ALMS, but most often becomes serious in adolescents or adults. Slowly progressive nephropathy, progressive glomerulofibrosis, and a gradual destruction of the kidneys are a major feature in adult patients with ALMS. Whether hypertension is a consequence of or contributes to renal dysfunction is uncertain, but it is present in ~30% of individuals [Marshall et al., 2005]. Patients may have symptoms ranging from chronic, mild kidney dysfunction to end-stage renal failure. Histopathologic changes include hyalinization of tubules and interstitial fibrosis [Goldstein and Fialkow, 1973, Marshall et al., 2005, 2007a]. There is evidence suggesting that the position of the alteration in *ALMS1* may play a r*o*le in the severity of the renal disease [Marshall et al., 2007b].

Hypogonadotropic hypogonadism

Male hypogonadotropic hypogonadism results in low plasma testosterone secondary to low plasma gonadotropin concentration. Males often have a small penis and testes, usually with gynecomastia in adolescence. Atrophic fibrotic seminiferous tubules are described [Marshall et al., 2007a]. Secondary sexual characteristics such as axillary and pubic hair are normal in both males and females. In female adolescents, sexual development usually progresses normally and menarche is not delayed (average age 12 years). In a few patients, precocious puberty has occurred (age 6–10) and breast development has been delayed. The external genitalia, uterus, and fallopian tubes are normal, but menstruation is often scant, sporadic, or irregular, sometimes accompanied by endometriosis. There can be reduced plasma gonadotropin concentrations. Baseline FSH and LH in female adolescents are usually in the normal range; however, some evidence of primary hypogonadism has been reported [Quiros-Tejeira et al., 2001]. Increased androgen production and hirsuitism are common [Kocova et al., 2010]. A relatively high frequency (>20% of female patients) of ovarian cysts is reported, which may be associated with obesity and hyperinsulinemia. No ALMS patients

have been known to reproduce – the few cases where this is „reported" are in patients without a confirmed molecular diagnosis [Boor et al., 1993].

Hypertriglyceridemia

Hyperlipidemia, particularly hypertriglyceridemia, can be present from early childhood. In some patients, a sudden, rapid rise in triglycerides places them at risk for pancreatitis [Paisey et al., 2009, Wu et al., 2002]. Other features in Alström Syndrome, such as hyperinsulinemia, may also contribute to the elevated triglycerides [Maffei et al., 2002, 2007].

2.1.2 Minor features

Hypothyroidism

A hypothyroid condition, mostly primary (low free thyroxine (FT4), high thyroid-stimulating hormone (TSH)), is observed in approximately 20% of patients [Michaud et al., 1996]. Subclinical hypothyroidisms in about 30% of patients and isolated incidents of hyperthyroidism have been observed [Ozgül et al., 2007]. The mechanism of the hypothyroidism remains unknown, although it could be hypothesized that fibrotic infiltrations in the thyroid gland play a role.

Dental abnormalities

Dental anomalies include discolored teeth, gingivitis, a large space between the front teeth, and extra or missing teeth [Koray et al., 2001].

Hands and feet

Most children have characteristic wide, thick, flat feet, and short stubby fingers and toes with no polydactyly or syndactyly. Rare cases of digit anomalies have been reported [Marshall et al., 2007a].

Urological dysfunction

Males and females with ALMS can experience varying degrees of urinary problems. Minor symptoms include urinary urgency, difficulty initiating or poor flow, long intervals between voiding, incomplete voiding (urinary retention) or abdominal pain before or during urination [Marshall et al., 2005]. There can be an unusual changing presentation, switching from retention to increased frequency, and incontinence. Recurrent urinary tract infections or cystitis are common in both males and females. Urethral strictures have also been described and fibrotic infiltrations have been noted histopathologically. A subset of patients have developed more severe complications such as marked frequency and urgency, incontinence, and significant perineal or abdominal pain requiring surgical intervention [Charles et al., 1990, Marshall et al., 2005, 2007a]. Anatomical abnormalities can also occur in ALMS, including calyceal deformities, narrowed ureteropelvic angles, dilated ureters, and misalignment of the kidneys [Ozgül et al., 2007].

Developmental delay

Although delay of cognitive impairment is not a common feature of ALMS, delay in early developmental milestones is seen in ~45% of affected children. Motor milestones, in particular sitting, standing, and walking, are typically delayed by 1–2 years and there may be deficits in coordination, balance, and fine motor skills. Hearing and vision deficits

probably contribute to the early developmental, expressive and receptive language, and learning delays seen in many young children with ALMS. Children with a receptive language deficit also tend to have an expressive language delay. Intellectual delays and behavioral issues in rare cases have resulted in a diagnosis of mental retardation. A range of autism-spectrum behavior has been observed in a subset of patients [Marshall et al., 2005, 2007a].

Other neurologic manifestations may include absence seizures and general sleep disturbances [Marshall et al., 2005, 2007a]. The frequency of mood and psychiatric disorders in ALMS-affected individuals has not been determined [Joy et al., 2007].

The combined effect of hearing loss and an accompanying multiple disabilities present a unique and complex problem to professionals and parents, different from the problems usually associated with any disability alone. A review of the literature yields surprisingly little specific information on educational programs for such children. The fact that there are many differences among children with multiple disabilities adds to the difficulties of providing appropriate programs.

2.2 Diagnostic criteria in Alström Syndrome

A major problem in arriving at a diagnosis of ALMS is the high phenotypic heterogeneity that can occur even within the same affected family [Ozgül et al., 2007, Hoffman et al., 2005 & Titomanilo et al., 2004]. Marshall and co-workers [Marshall et al., 2007a] provided a comprehensive guidance for diagnostic criteria in their 2007 publication, as summarized below:

Birth – 2 years: Diagnosis requires 2 major or 1 major and 2 minor criteria	
Major criteria:	1) *ALMS1* mutation in 1 allele and/or family history of Alström Syndrome 2) Vision pathology (nystagmus, photophobia).
Minor criteria:	1) Obesity 2) DCM with CHF.
Other variable supportive evidence	Recurrent pulmonary infections, normal digits, delayed developmental milestones.

3–14 years of age: diagnosis requires 2 major criteria or 1 major and 3 minor criteria	
Major criteria:	1) *ALMS1* mutation in 1 allele and/or family history of Alström Syndrome 2) Vision pathology (nystagmus, photophobia, diminished acuity). If old enough for testing: cone dystrophy by ERG.
Minor criteria:	1) Obesity and/or insulin resistance and/or T2DM 2) History of DCM with CHF 3) Hearing loss 4) Hepatic dysfunction 5) Renal failure 6) Advanced bone age

Other variable supportive evidence	Recurrent pulmonary infections, normal digits, delayed developmental milestones, hyperlipidemia, scoliosis, flat wide feet, hypothyroidism, hypertension, recurrent urinary tract infections, growth hormone deficiency
15 years – adulthood: 2 major and 2 minor criteria or 1 major and 4 minor criteria	
Major criteria:	1) ALMS1 mutation in 1 allele and/or family history of Alström Syndrome 2) Vision pathology (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG).
Minor criteria:	1) Obesity and/or insulin resistance and/or T2DM 2) History of DCM with CHF. 3) Hearing loss 4) Hepatic dysfunction 5) Renal failure 6) Short stature 7) Males: hypogonadism. Females: irregular menses and/or hyperandrogenism
Other variable supportive evidence	Recurrent pulmonary infections, normal digits, history of developmental delay, hyperlipidemia, scoliosis, flat wide feet, hypothyroidism, hypertension, recurrent urinary tract infections/urinary dysfunction, growth hormone deficiency, alopecia.

Table 1.

In conclusion, ALMS is a very complex disorder, being characterized by a constellation of progressive and highly variable disease symptoms. Diagnosis is made on the basis of clinical features observed, usually without genetic confirmation. Delay of onset of some of the characteristic features (type 2 diabetes mellitus, DCM/chronic heart failure, hepatic dysfunction, pulmonary, and renal disease) makes early differential diagnosis very difficult in young children, as many of the cardinal features do not become apparent until the teenage years. As the child grows, the characteristic pattern of ALMS evolves and the clinical picture becomes clearer.

2.3 Age of onset and incidence of common features of Alström Syndrome

Marshall and co-workers [Marshall et al., 2005] described the age of onset and the incidence of common features of Alstrom syndrome. Cone-rod dystrophy was diagnosed in 100% of ALMS patients between birth and 15 months. Obesity usually begins to develop during the first year, birth weight being normal. Hearing loss is progressive and presents in 88% of cases during the first 9 years. Dilated cardiomyopathy could be diagnosed in 42% of infants under 4 months of age. In adolescents and adults the pattern is often restrictive cardiomyopathy, with an overall incidence of 18%. Insulin resistance/type 2 diabetes can be diagnosed in children as young as 4 years of age. While urologic dysfunction can be seen at any age, chronic renal failure begins in adolescents and adults. About 25-30 % of ALMS

patients are diagnosed with developmental delay, based on the assessment of early development milestones. Liver involvement develops variabily, between 8 and 30 years of age, in 23-98% of patients. Over 98% are diagnosed with short stature after puberty or in adulthood. Among the endocrine abnormalities, hypogonadotropic hypogonadism was diagnosed in 78% of males.

2.4 Genetic diagnosis

Alström Syndrome is the consequence of recessively inherited mutations in a single gene, *ALMS1,* located on the short arm of chromosome 2 [Collin et al., 2002, Hearn et al., 2002]. Parents are obligate carriers of a single copy of the altered gene and have no reported heterozygous phenotypic characteristics. Males and females are affected with equal probability (1:1 ratio). Although the incidence is greater in isolated or consanguineous communities, there is no one ethnic group more likely to carry *ALMS1* mutations [Marshall et al, 2007a].

ALMS1 is comprised of 23 exons. The longest *ALMS1* transcript potentially encodes a 461 kDa protein of 4169 amino acids. Exon 1 contains a tract of glutamic acid residues (aa 13–29), followed by a stretch of seven alanine residues (aa 30−36) [Collin et al., 2002, Hearn et al., 2002]. Exon 8, a large 6-kb exon, contains a large tandem repeat domain encoding 34 imperfect repeats of 45–50 amino acids. This domain constitutes 40% of the protein, a short polyglutamine segment, a leucine zipper domain and a conserved motif near the C-terminus.

The *ALMS1* protein is ubiquitously expressed and at least one isoform localizes to centrosomes and basal bodies of ciliated cells, perhaps playing an important role in cilia function and intraflagellar transport [Collin et al., 2005, Hearn et al., 2005; Knorz et al., 2010]. RNA interference knockdown experiments indicate that a total lack of *ALMS1* impairs cilia formation [Li G et al., 2007].

To date, the mutations reported in *ALMS1* have been nonsense and frameshift variations (insertions or deletions) and one reciprocal translocation that are predicted to cause premature protein truncation [Collin et al., 2002, Hearn et al., 2002]. Since 2002, more than 100 different mutations in *ALMS1* have been identified. The variants are primarily clustered in exons 16, 10, and 8, but less common mutations also occur in exons 12 and 18 [Marshall et al., 2007a; Joy et al., 2007; Pereiro, et al., 2010]. Founder effects are reported in families of English and Turkish descent. In addition, numerous single-nucleotide polymorphisms have been identified, the functional significance of which is unclear [Marshall et al., 2007a]. The mechanisms by which disease alleles of *ALMS1* cause the various pathologies observed in Alström Syndrome remain unknown and identification of pathogenic mutations in *ALMS1* has not led to any genotype-specific treatments [Hearn et al., 2005, Kinoshita et al., 2003, Li G et al., 2007, Minton et al., 2006 & Patel et al., 2006].

ALMS1 RNA is widely expressed by many tissues. Splice variants have been identified from human brain and testis which may suggest differing functions of theALMS1 protein between organs [Hearn et al., 2002].

The ubiquitous expression of *ALMS1* correlates with the wide range of organ dysfunction in ALMS and suggests that the C-terminal portion of the Alms1 protein that is missing in ALMS patients plays a critical role in disease causation [Girard & Petrovsky, 2010]. Because *ALMS1* is a very large gene, complete sequencing is time consuming and expensive. Therefore, we recommend a screening strategy that targets the regions of *ALMS1* where most of the mutations are seen (exons 16, 10, part of 8). If no mutation is identified in these

areas, the remaining genomic regions can be sequenced on a research basis. The sensitivity of this approach is approximately 65%, that is, in about 42% of all patients both mutations will be detected, in about half of the patients, only one of the two mutations will be found, and in about 10% of the patients, none of the mutations will be found. The recent development of an-ALMS mutation array to detect known mutations in *ALMS1* (Asper Biotech (www.asperbio.com) can be used as an efficient and cost-effective first pass screening for known mutations *ALMS1* and 10 known Bardet-Biedl Syndrome (BBS) genes [Pereiro et al.,2010]. New technological developments including target capture and next generation sequencing will offer the possibility of efficient and cost-effective identification of novel *ALMS1* mutations and for carrier testing [Bell et al., 2011]

The possible results of genetic testing must be interpreted within the context of the clinical picture [Marshall et al., 2007a]:

- 2 mutations identified in ALMS1. Diagnosis: ALMS.
- 1 mutation in *ALMS1* together with clinical signs of Alström Syndrome. Diagnosis: very strong evidence for the confirmation of ALMS (although about 0.25% of all healthy individuals could also show this result).
- No ALMS1 mutation identified. This does not exclude the diagnosis, in the presence of clinical manifestations suggestive for ALMS.

3. Differential diagnosis of Alström Syndrome [Marshall et al., 2007a]

	Alström Syndrome	*Bardet–Biedl Syndrome (BBS #1-14)*	*Congenital achromatopsia*	*Leber congenital amaurosis (LCA)*	*Wolfram (DIDMOAD)*	*Cohen Syndrome*	*Biemond II Syndrome*
OMIM	203800	209900	216900 262300 139340	204000	222300	216550	210350
Vision	Cone dystrophy, photophobia	Night blindness, rod–cone dystrophy (age 10–16)	Cone dystrophy	Cone dystrophy (infancy)	Optic atrophy	Rod–cone dystrophy >5 years myopia, bulls-eye maculopathy, peripheral vision loss	Coloboma, microphthalmia, aniridia, cataract
Cardiac	Yes	Congenital heart defects (5–10%)	No	No	No	No	No

Mental development	Hypogonadism	Diabetes	Obesity	Renal	Neurosenso hearing loss
Normal/delayed	Yes	T2DM (90%)	Yes	Glomerulo-sclerosis	Yes (90%)
Mental retardation (50%)	Yes	T2DM (5–15%)	Yes	Structural renal abnormalities	Yes (5–20%)
Normal/ delayed	No	No	No	No	No
Normal/ delayed	No	No	No	No	No
Normal, behavior problems	No	Diabetes insipidus, insulin-dependent diabetes mellitus	No	Diabetic nephropathy	Yes
Moderate-to-severe delay	No	No	Yes, abdominal obesity, thin arms and legs	No	No
Mental retardation	Yes	No	Yes	No	No

Table 2.

Genetic	Head	Orthopedic	Urologi
ALMS1 (2p13)	No	Short fingers, wide flat feet, scoliosis	Varying degrees o urinary problems
BBS1, *BBS2*, *ARL6/BBS3*, *BBS4*, *BBS5*, *MKKS/BBS6*, *BBS7*, *TTC8/BBS8*, *B1/BBS9*, *BBS10*, *TRIM32/BBS11*, *BBS12*, *MKS1/BBS13*, *CEP290/BBS14*.	High-arched palate, hypodontia	Poly-, brachy-, and syndactyly	
CNGA3 CNGB3GNAT2	No	Normal	
GUCY2D (LCA1), *RPE65* (LCA2), *SPATA7* (LCA3), *AIPL1* (LCA4), *LCA5* (LCA5), *RPGRIP1* (LCA6), *CRX* (LCA7), *CRB1* (LCA8), *CEP290* (LCA10), *IMPDH1* (LCA11), *RD3* (LCA12), and *RDH12* (LCA13).	No	Normal	
WFS1 (4p16)	No	Normal	Urinary a
COH1 (8q22)	Characteristic facial features	Narrow hands and feet, tapered fingers	
	Absent incisors, microcephaly, characteristic facial features	Postaxial polydactyly, scoliosis	

4. Management

There is no treatment at this time that can cure ALMS or prevent or reverse the medical complications.
Early diagnosis is important to allow counseling of parents and institution of appropriate supportive medical treatment. In the absence of specific therapy to correct the underlying genetic defect, ALMS remains a progressive disease and regular intensive medical management is essential to track progression and to anticipate the emergence of new symptoms and disease manifestations.
Cardiac, renal and liver review should be routinely performed in all ALMS patients, even if asymptomatic.
The main causes of death in ALMS are from cardiomyopathy, pulmonary, kidney or liver failure [Marshall et al., 2005, Benso et al., 2002]. In the end stage, multiple organs are compromised, and sudden multiple organ failure is common.

4.1 Management of sensory deficits

Vision and hearing loss can impact the social and educational success of the child, so, management of the multiple sensory deficits in young children diagnosed with ALMS and social support at school are crucial [Marshall et al., 2007a].

4.1.1 Rod-cone dystrophy

Photophobia and nystagmus are serious problems, particularly in younger children. Regular ophthalmologic evaluations should be sought as soon as possible [Gogi et al., 2007]. Red-tinted prescription glasses are helpful in alleviating the distress children experience in bright lighting. No therapy for the progressive vision loss exists, but early evaluation of visual acuity facilitates the provision of visual aids and helps prepare the child for a future with little or no sight. Educational planning should anticipate future blindness, therefore, early mobility training and Braille or other non-visual language skills is critically important for the learning environment of the child. Computing skills (including voice recognition and transcription software), and the use of large print reading materials early on while vision is still present are crucial [Marshall et al 2010].

4.1.2 Progressive sensorineural hearing loss

Hearing evaluation should begin early in childhood, as otoacoustic emissions and audiometry may reveal subclinical hearing loss. Conductive loss is common in children as a result of chronic otitis media. Hearing can usually be effectively managed with bilateral digital hearing aids, but should be monitored regularly. Myringotomy has been helpful in individuals with recurrent "glue ear". Cochlear implantation has benefitted some patients, but surgeons should be aware of the risk of sudden hypoxia for these patients undergoing procedures requiring anesthesiology [Florentzson et al., 2010].

4.2 Obesity. Insulin resistance/Type 2 diabetes

The major clinical treatment focus is on control of obesity and T2DM.
Candidate therapeutic intervention to treat severe insulin resistance and possibly prevent the transition from insulin resistance to overt diabetes include insulin-sensitizing drugs (metformin and thiazolidinediones) [Sinha et al., 2007 as cited in Atabek, 2007, Nag S et al.,

2003] and beta cell-preserving drugs (incretins, thiazolidinediones) [Pagano et al., 2008, Paisey et al., 2009]. However, this requires close monitoring of liver, cardiac, and renal function. Glitazones are added to further reduce insulin resistance but must be avoided in the presence of active or treated heart failure and when the serum creatinine concentration exceeds 200 μmol/L. Exenatide, an incretin mimetic, an injectable analogue of glucagon-like peptide 1(GLP- 1) could be promising in adults with ALMS.

Weight loss exercises should play a pivotal role in weight reduction plan for ALMS patients, as in other patients diagnosed with dibetes and obesity, although could be challenging. Walking, hiking, biking, and swimming with partners and adaptations for the blind have been helpful. Peripheral sensor-motor neuropathy is a common complication of T2DM, but in a small clinical testing study in ALMS, a full preservation of protective foot sensation was demonstrated [Paisey et al., 2009]. The responsiveness to treatment of hyperglycemia is variable. Younger patients rarely require insulin, but some patients require insulin in very-high doses long term [Marshall et al., 2007a].

Caloric restriction helps control obesity, glucose tolerance and hyperinsulinemia [Holder et al., Lee et al., 2009 & Paisey et al. 2008], although as with children with other genetically acquired obesity syndromes, dietary compliance may be a major problem. Reducing dietary carbohydrates may prove more effective than fat restriction in control of hyperglycemia and hyperinsulinemia [Paisey et al., 2008]. No clinical experience has been reported in ALMS of use of specific appetite suppressant medication, such as duramine or sibutramine.

4.3 Hypertriglyceridemia

Insulin resistance, T2DM, dyslipidaemia and associated cardiac, renal and hepatic consequences coexist from a young age with considerable morbidity and reduction in life expectancy. ALMS patients can have potentially harmfully increased lipid levels. Hypertriglyceridemia can often be normalized by diet, exercise and Metformin. Some patients with severe hypertriglyceridemia responded to a combination of low-fat diet, statins and nicotinic acid [Paisey et al., 2004], very little data existing, however, about the safety and efficacy of such treatments before puberty.

Early introduction of preventative nutrition with low-carbohydrates, exercise and drug therapies (niacin extended-release and incretins) in ALMS could be beneficial [Paisey, 2009].

Pancreatitis should be treated as in the general population, but it is a challenge to treat a patient with multiple system involvement such as ALMS patients [Marshall et al., 2010, Paisey, 2009, Wu WC et al., 2003].

4.4 Impaired growth hormone (GH)-IGF1 axis function

There is an impaired growth hormone (GH)-IGF1 axis function in ALMS (Maffei et al., 2000, 2002), therefore, therapy with recombinant human Growth Hormone (rhGH) has been attempted in a small series of patients and isolated cases and has been reported to be beneficial for some metabolic parameters. Demonstrating growth hormone deficiency in a patient with ALMS, Tai and co-workers assessed the metabolic effects of growth hormone therapy concluding that rhGH therapy might have beneficial effects on body composition, liver fat content, lipid profiles, and insulin resistance in Alström Syndrome patients, with improvement of the glucose homeostasis [Tai et al., 2003]. Also, Maffei et al. found a reduction of ALS (acid labile subunit) and the increase of IGFBP-2 as expression of growth

hormone deficiency condition in 15 young adults with ALMS [Maffei et al., 2000]. RhGH therapy should be considered still investigational [Marshall et al. 2007a]. Several studies are needed to prove that this therapy is cost-effective and without risk in patients with ALMS and severe insulin resistance.

4.5 Cardiomyopathy

Patients diagnosed with ALMS should be regularly monitored for cardiac function by echocardiography, even if asymptomatic [Makaryus et al., 2002, Zubrow et al., 2006]. Several authors [Loudon et al., 2009, Makaryus et al., 2007] stated the importance of serial cardiac magnetic resonance scanning in diagnosis of the underlying disease progression and responses to treatment. Long-term angiotensin-converting enzyme inhibition is indicated for the patient with cardiomyopathy. Many patients respond to other medications, which favorably affect heart function, such as diuretics, digitalis, beta-blockers, and spironolactone. Whether cardiac transplantation is a viable option is yet to be determined, due to the multisystemic involvement, particularly pulmonary, endocrine, and renal function. There has been one successful heart-lung transplantation reported in an adolescent patient with Alström Syndrome, but with no T2DM or significant renal failure [Görler et al., 2007]. A second successful heart transplant has been achieved in an infant prior to the onset of the endocrinological and renal disturbances [JD Marshall, Personal communication].

4.6 Thyroid

Replacement therapy with L-thyroxin, when needed, is very effective and well-tolerated in the majority of patients.
Thyroid function should be monitored closely in critical hospital settings [Marshall et al., 2007].

4.7 Urologic

Lack of coordination between bladder and urine outflow (detrusor-urethral dyssynergia) can be helped by intermittent self-catheterization of the bladder. Ileal diversion may be necessary in rare patients [Marshall et al., 2007; Charles, et al. 1990].

4.8 Hypogonadotropic hypogonadism

If abnormalities in pubertal development or menstrual abnormalities are present, the affected individual should be referred to an endocrinologist with expertise in sexual developmental abnormalities. Primary hypogonadism in ALMS males result in low levels of testosterone, treated with weekly or twice monthly injections of testosterone from puberty onwards. Treatment with cyclical oestrogen and progesterone is important and effective to regulate menstrual cycle and development.

4.9 Hepatic disease

Liver function parameters should be routinely monitored, beginning in childhood. Portal hypertension and varices may be aggressively treated with beta-blockers and sclerotherapy of the esophageal veins. Variceal banding could be useful to prevent upper gastro-intestinal hemorrhage. A transjugular intrahepatic portosystemic shunt (TIPS) is used to treat the complications of portal hypertension, when the patient has failed to respond to previous therapeutic measures. Patients with significant portal hypertension should be evaluated early for liver transplantation [Marshall et al., 2007].

4.10 Renal disease

Because renal insufficiency develops slowly as the patient ages, regular testing of renal function (plasma electrolytes, blood urea nitrogen, creatinine, and urea) is important, particularly in the older patient. Baseline values should be taken in children. Management of hypertension, a low-sodium and low-protein diet, avoidance of nephrotoxic drugs are very important in the preservation of renal function, as well as angiotensin-converting enzyme inhibitors prescribed according to general guidelines. Fibrosis and glomerulosclerosis in the kidneys may lead to eventual renal failure, requiring dialysis. Renal transplantation has been successful in several patients, although can be contraindicated in the presence of other complications including morbid obesity, uncontrolled diabetes, and cardiomyopathy [Marshall et al., 2007].

4.11 Pulmonary disease

Pulmonary fibrosis, dilated cardiomyopathy, and scoliosis can compromise cardio-respiratory function, particularly with concomitant respiratory infection or anesthesia in routine surgical procedures. Monitoring cardiac status and oxygenation during acute illness and postoperatively are mandatory, considering that ALMS patients can suddenly, without warning become critically hypoxic [Lynch et al., 2007, Tiwari et al., 2010]. Chronic obstructive airway disease and associated infection should be managed in line with appropriate national guidelines.

4.12 Other

4.12.1 Gastrointestinal

Reflux esophagitis should be diagnosed by barium swallow or upper gastrointestinal endoscopy, in the presence of suggestive symptoms and treated accordingly to the guidelines.

4.12.2 Orthopedic abnormalities

In the presence of flat feet, scoliosis, barrel chest, kyphoscoliosis the referral to an orthopedist is appropriate. Some patients have had surgical intervention for scoliosis, but care should be taken when undertaking surgical procedures, as previously mentioned.

4.12.3 Neurologic manifestations

ALMS patients should be examined for: absence seizures, autistic-spectrum behavioral abnormalities, excessive startle, unexplained joint or muscle pain, muscle dystonia, or hyporeflexia.

4.13 Prevention of secondary complications

There should be routine pediatric immunizations, especially against flu and hepatitis B virus infections.

Families should be encouraged to seek contact with good sources of support and information, such as Alström Syndrome International (www.alstrom.org) or other groups assisting families with this rare disorder.

5. Conclusion

Full understanding of the phenotypic characteristics, particularly with the help of existing mouse models [Collin et al., 2005, Arsov et al., 2006a, 2006b] will lead to better insight into

the pathophysiology of *ALMS1.* By developing targeted therapies, certain debilitating aspects of ALMS could be prevented or treated earlier, improving the overall outcome in this complex disorder [Marshall et al., 2007]. Also, careful clinical and genetic studies can contribute to a better understanding of the disease evolution after different therapeutic attempts in Alström Syndrome.

6. References

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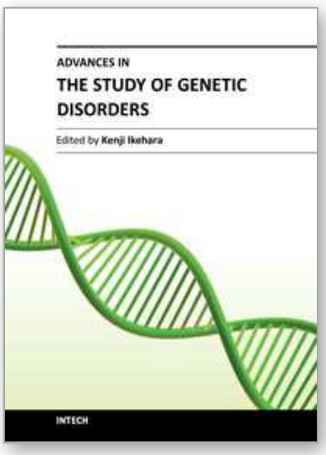

Advances in the Study of Genetic Disorders

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The studies on genetic disorders have been rapidly advancing in recent years as to be able to understand the reasons why genetic disorders are caused. The first Section of this volume provides readers with background and several methodologies for understanding genetic disorders. Genetic defects, diagnoses and treatments of the respective unifactorial and multifactorial genetic disorders are reviewed in the second and third Sections. Certainly, it is quite difficult or almost impossible to cure a genetic disorder fundamentally at the present time. However, our knowledge of genetic functions has rapidly accumulated since the double-stranded structure of DNA was discovered by Watson and Crick in 1956. Therefore, nowadays it is possible to understand the reasons why genetic disorders are caused. It is probable that the knowledge of genetic disorders described in this book will lead to the discovery of an epoch of new medical treatment and relieve human beings from the genetic disorders of the future.

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