New Alström Syndrome Phenotypes
Based on the Evaluation of 182 Cases

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Background: Alström syndrome is a recessively inherited genetic disorder characterized by congenital retinal dystrophy that leads to blindness, hearing impairment, childhood obesity, insulin resistance, and type 2 diabetes mellitus. We provide new details on cardiologic, hepatic, gastrointestinal, urologic, pulmonary, and neurobehavioral phenotypes in Alström syndrome and describe the histopathologic findings in 5 individuals.

Methods: We obtained data on 182 patients from clinical examinations, medical record reviews, standardized questionnaires, and personal interviews with physicians and parents.

Results: Dilated cardiomyopathy occurred in 60% of patients. Age at onset was either during infancy, often before vision disturbances were noted, or in adolescence or adulthood. There is a risk of recurrence of infantile cardiomyopathy. Hyperinsulinemia (92%) developed in early childhood and progressed to type 2 diabetes mellitus in 82% of those older than 16 years. Hypertriglyceridemia (54%) precipitated pancreatitis in 8 patients. Urologic dysfunction and gastrointestinal disturbances occurred in 48% and 35% of patients, respectively. Fifty-three percent of patients had persistent pulmonary symptoms. Neurologic symptoms in 20% of patients included clonic tic and absence seizures. Developmental motor or language delays were observed in 46% of patients. Fibrotic infiltrations of multiple organs, that is, kidney, heart, liver, lung, urinary bladder, gonads, and pancreas, were observed.

Conclusions: The wide-ranging and complex spectrum of phenotypes reported herein broadens those previously described for Alström syndrome. These findings will aid physicians in making an early and accurate diagnosis and will help effect appropriate monitoring and treatment.

Arch Intern Med. 2005;165:675-683
304 patients with Alström syndrome worldwide. We collected sufficient clinical information to include 182 of these patients in this study. Although some patients have been followed up for up to 12 years, the amount of information available for each varies. If a condition was not reported by parents or medically documented, we inferred that it was not present. Because some evaluations are not routinely performed, the true prevalence of some phenotypes may be higher than reflected herein.

Samples of DNA were available for mutational analysis from 130 of 182 patients. Thus far, mutations in at least 1 allele of ALMS1 have been identified in 63 patients; 36 additional patients had 2p13-specific haplotypes consistent with linkage. We examined the cardinal features and new phenotypes in patients whose diagnosis was confirmed genetically and in 86 patients whose conditions were clinically diagnosed by phenotypic evaluation. All features were present in both groups. We obtained written informed consent from all participants or parents of minors. The institutional review board of The Jackson Laboratory and the ethical review committee of Alström Syndrome International independently approved the study protocols. No financial remuneration was given to patients or families for participation in this study.

CLINICAL EXAMINATIONS

Patient assessment included ophthalmologic, audiologic, and general physical examinations. We obtained blood samples using standard venipuncture techniques after an overnight fast. Serum chemistries and routine urinalysis were performed using traditional methods in licensed clinical laboratories.

A fasting glucose level of 110 to 126 mg/dL (6.1-7.0 mmol/L) or a 2-hour level of 140 to 200 mg/dL (7.8-11.1 mmol/L) in response to an oral glucose challenge or basal hyperinsulinemia (insulin level >15 µU/mL [>104 pmol/L]) was evidence of impaired glucose tolerance. Glucose levels greater than 126 mg/dL (7.0 mmol/L) or glycosylated hemoglobin levels greater than 7% of total hemoglobin indicated diabetes mellitus. We interpreted elevated thyrotropin levels in the presence of normal triiodothyronine and hemoglobin indicated diabetes mellitus. We interpreted elevated thyrotropin levels in the presence of normal triiodothyronine and thyroxine levels as "subclinical hypothyroidism," and elevated creatinine (≥2.0 mg/dL [≥152 µmol/L]) or blood urea nitrogen (≥20 mg/dL [≥7.1 mmol/L of urea]) levels or proteinuria was evidence of renal insufficiency. Bone age was assessed using the scales of Greulich and Pyle. Pubertal onset was defined as a testicular size greater than 4 mL in boys and a Tanner 2 breast stage in girls. We considered male hypogonadism as a stretched penis of less than 4 cm in prepubertal boys and of less than 9 cm in adults. Amenorrhea was defined as the absence of menarche in girls older than 15 years or cessation of menstruation for at least 6 months. Patients with hypertension had arterial pressure greater than 140/90 mm Hg (adults) and 130/80 mm Hg (patients aged 18 years).

PSYCHOMOTOR DEVELOPMENT, BEHAVIOR, AND INTELLIGENCE TESTING

We estimated mentation and neurobehavioral traits based on the level of school and social performance and interviews with parents. Intelligence tests included the Wechsler Adult Intelligence Scale—Revised, the Bayley Scales of Infant Development II, Birth to Three Test of Language and Learning Development, Behavior Assessment System for Children, and the Haptic Intelligence Scale for the Adult Blind. The ages at which children first sat, walked, and organized phrases of at least 2 words were used as psychomotor developmental milestones during childhood.

PATHOLOGY SAMPLES

We obtained postmortem tissue samples and pathology reports from 3 women and 2 men aged 27 to 42 years. Autopsies were performed in local hospitals 5 to 13 hours after death. Tissues were preserved in 10% formalin/90% ethanol and were processed according to standard protocols.

STATISTICAL ANALYSIS

χ² and paired t tests were used for comparisons between groups. We used 2 statistical analysis programs: SPSS for Windows, version 10.0.5 (SPSS Inc, Chicago, Ill) and JMP version 5.0.1 (SAS Institute Inc, Cary, NC).

RESULTS

PATIENT POPULATION

Alström syndrome has multinational geographic distribution among diverse racial and ethnic groups. Twenty-one infants with limited clinical records died between ages 5 days and 16 months: 19 had CHF or other cardiac complications, and in 2 the cause of death was undetermined. The reported symptoms and at least 1 other affected sibling suggest Alström syndrome as the most likely diagnosis for these patients.

The remaining 161 patients (78 females and 83 males; age range, 18 months to 48 years) includes 88 new patients and 47 kindreds previously described. The sanguinity rate was 30%. Thirty-one of the 161 patients died during study observation: 12 of CHF (age range, 10-27 years), 7 of renal failure (age range, 22-48 years), 4 of pulmonary failure (age range, 29-42 years), 3 of liver failure (age range, 21-32 years), and 5 of undetermined causes (age range, 9-48 years).

ALSTRÖM SYNDROME PHENOTYPES

Frequency, mean age at onset, and age range of clinical features that were observed in our patient population are shown in Figure 1.

Neurosensory

Nearly all patients (98%) developed pendular or searching nystagmus and photodysesthesia during the first year of life (age range, birth to 40 weeks) and reduced visual acuity in childhood. All patients older than 15 years were legally blind. Electroretinograms initially showed an absence of cone function and progressive deterioration of rod function. Degeneration of the retinal pigment epithelium, poorly defined macula consistent with cone-rod dystrophy, attenuated vessels, and optic disc pallor were reported. Subcapsular cataracts were present in 52 patients (32%; age range, 10-44 years).

Mild-to-profound bilateral sensorineural, predominantly high-frequency, hearing impairment evolved throughout childhood (89%; age range, 2-21 years; mean age at onset, 5 years). Chronic otitis media and glue ear, particularly frequent in patients younger than 12 years, resulted in additional conductive hearing loss in 68 (42%) of 161 patients.

Anthropomorphic Measurements

Most children had rapid growth, with height above the 50th percentile before puberty but final adult height below the
5th percentile (Figure 2A and B). The mean ± SD height of patients older than 16 years was 158.7 ± 0.9 cm in males (n = 40) and 150.4 ± 1.5 cm in females (n = 46). Childhood obesity occurred in 158 (98%) of 161 patients. Although mean ± SD birth weight was within the reference range (2998 ± 518 g; n = 53), rapid weight gain was observed within 2 to 36 months, with a mean age at onset of 18 months (Figure 2C and D). Body mass index (calculated as weight in kilograms divided by the square of height in meters) ranged from 21 to 53 in males (n = 69) and from 24 to 51 in females (n = 63) (Figure 2E and F). Obesity in some patients moderated with the onset of other clinical complications. The presence of hyperphagia was inconclusive from food intake records (n = 26; age range, 4-35 years).

Physical Features

Skeletal age was 1 to 3 years in advance of chronologic age in children younger than 16 years (n = 28). Thoracic and lumbar scoliosis, kyphosis, or lordosis was present in 110 (68%) of 161 patients (age range, 4-42 years). Fingers tended to be short and tapered. The children had characteristic short, thick, wide, and flat feet (Figure 3). Polydactyly was absent in 158 (98%) of 161 patients. Three patients fulfilled the diagnostic criteria but had digital abnormalities. One child was born with 2 clubfeet, and another had postaxial polydactyly. Both of these patients had affected siblings with normal digits. The third patient with polydactyly had a confirmed mutation in ALMS1 (G.B.C., written communication, 2004). Craniofacial features included deep-set eyes and slightly hyperplastic ears. Dental abnormalities in 33% of patients consisted of a pronounced gap between the upper front teeth, crowding, late eruption, and selective brown enamel discoloration. Twenty-six males (age range, 14-32 years) and 20 females (age range, 7-48 years) (29%) had alopecia.

Endocrine

Hyperinsulinemia usually developed between ages 18 months and 4 years (92%). Most patients were insulin resistant or glucose intolerant (n = 117; age range, 2-48 years); 110 patients (68%) developed acanthosis nigricans (age range, 5-48 years). Type 2 diabetes mellitus was diagnosed as early as age 5 years, with a median age at onset of 16 years. Eighty-two percent of patients older than 16 years were diabetic. Most patients had moderate to severe hypertriglyceridemia (triglyceride level, 200-1000 mg/dL [2.26-11.29 mmol/L]), with normal total cholesterol levels (n = 80; age range, 2-42 years). Eight patients developed acute pancreatitis (age range, 18-26 years), with triglyceride levels greater than 10000 mg/dL (>112.90 mmol/L). Hypothyroidism was observed in 28 (36%) of 78 patients measured (age range, 8-42 years), and 20 additional patients (age range, 4-37 years) had subclinical hypothyroidism.

Gonadal

Hypergonadotropic and hypogonadotropic hypogonadism were common in males (64/83; 77%). Puberty was often delayed, but masculinization and secondary sexual characteristics in adult males were normal (n = 35). The most frequent observation was diminished basal testosterone levels for age and increased baseline luteinizing hormone/follicle-stimulating hormone levels typical of primary gonadal failure (age range, 16-32 years). Gynecomastia was present in 31 males, and cryptorchidism was present in 2. Mean menstrual age was 12.6 years (n = 36). Endocrine disturbances in 42 (54%) of 78 females included hirsutism, abnormal breast development, cystic ovaries, precocious puberty (pubertal onset at age <8 years), endometriosis,
irregular menses, or amenorrhea. External genitalia were normal in those females examined (n=42). No patients in this study have reproduced.

Cardiac

Seventy (38%) of 182 patients have had no signs of cardiac failure to date (age range, 2-33 years), although the risk remains for developing DCM in the future. Dilated cardiomyopathy occurred in 112 patients (62%) (Figure 4). These patients can be divided into 2 groups: infant onset and adult onset. Seventy-nine patients (43%) had DCM and CHF in infancy (age range, 1 week to 16 months). Most of these infants (57 of 77) survived, with apparent atypical recovery of cardiac function within 3 years. Although previous studies suggest that infants who survived DCM had progressive improvement in cardiac function with no evidence of long-term negative effects, we found that after a variable interval of normal cardiac function, 24 of these patients experienced an abrupt recurrence of DCM between ages 5 and 36 years, and 10 have died. The reappearance of CHF in a growing number of these patients suggests that cardiac function should be regularly monitored. A second group of 33 (18%) of the 182 patients had no cardiac history in infancy but developed DCM as adolescents or adults (age

**Figure 2.** Anthropometric measurements in patients with Alström syndrome. Mean ± SEM height in males (A) and females (B); weight in males (C) and females (D); and body mass index (BMI) in males (E) and females (F) compared with controls. Control values for the 5th, 10th, 25th, 50th, 75th, and 95th percentiles (gray lines) were taken from stature-for-age, weight-for-age, and BMI-for-age percentile charts (http://www.cdc.gov) and from Najjar and Rowland.25
range, 7-32 years). These patients have a poor clinical prognosis; 11 of 33 have died (age range, 14-48 years).

**Hepatic and GI**

There was mild to severe elevation in liver transaminase levels as early as age 4 years in 89 (92%) of 97 patients tested. Hepatomegaly and splenomegaly were observed in patients as young as 8 years. Biopsies revealed hepatic steatosis, inflammation, bridging fibrosis, and cirrhosis (n=16). Portal hypertension resulted in hemorrhaging esophageal and gastric varices (n=14; age range, 14-37 years). Two patients required a surgical transjugular intrahepatic portosystemic shunt at ages 18 and 32 years, respectively. General GI disturbances in 57 patients (35%) included frequent upper GI pain, chronic diarrhea, and constipation; gastroesophageal reflux was diagnosed, based on findings from either upper GI series or endoscopies, in 35 patients.

**Urologic and Renal**

General urologic disturbances and abnormal voiding patterns were reported in 57 females and 20 males (48%). Recurrent urinary tract infections were common (age range, 2-40 years) in males and females. Premicturition discomfort, difficulty initiating voiding, poor flow, long voiding intervals, retention, urgency, and urge incontinence suggested a variable decrease in bladder sensation and activity or, conversely, overactivity. Six females aged 17 to 19 years had initial urinary retention followed, 6 to 12 months later, by detrusor overactivity, incontinence, and substantial lower abdominal and perineal pain that required anticholinergic medication use, self-catheterization, or surgical urinary diversion. The change from a voiding pattern of hyporeflexia to bladder overactivity, urgency to void, and incontinence is unusual, and the reasons for it are not understood. There was no association between urinary tract infection \( (P = .83) \) or bladder activity issues \( (P = .52) \) with kidney function or any indication that vesicoureteral reflux causes the renal damage in patients with Alström syndrome. Renal insufficiency was observed in 80 (50%) of 161 patients (age range, 5-42 years). Renal function declined as patients aged, and end-stage renal disease was the cause of death in 7 patients. Forty-eight patients (30%) were hypertensive, some as young as 2 years (age range, 2-42 years). Three patients have undergone successful kidney transplantation.

**Pulmonary**

Chronic asthma; sinusitis; bronchitis; a dry, barking cough; and alveolar hypoventilation with reduced forced expiratory volume in 1 second were reported in 85 (33%)
of 161 patients (age range, 2-42 years). Multiple bouts of bronchopneumonia were a frequent finding. More severely compromised lung function in 39 patients (24%; age range, 10-48 years) included lower airway obstruction with consolidation and with acute inflammation, chronic obstructive pulmonary disease, acute (adult) respiratory distress syndrome, and emphysema. Diffusing capacity of the lung for carbon monoxide, ground glass opacification, or lung biopsies revealed structural fibrotic changes (n=6; age range, 10-40 years). None of the patients in this study smoked.

Neurobehavioral

Developmental milestones were delayed in 39 males and 35 females (46%). Fine and gross motor skill and mixed receptive-expressive language delays were reported. Autistic-spectrum behavioral abnormalities, excessive startle, partial unilateral paralysis, unexplained joint or muscle pain, muscle dystonia, and hyporeflexia were observed in 33 patients (20%; age range, 9 months to 41 years). Twenty of these patients had frequent absence seizures. Birth complications included neonatal hypoxia and hypotonia (n=26). Twenty-five patients (16%) had generalized sleep disturbances (age range, 3-41 years); 4 had obstructive sleep apnea.

Pathologic Findings

The Table describes the clinical condition of 5 patients from whom pathologic specimens were available. Glomerular and interstitial renal fibrosis was observed in all 5 patients. Affected glomeruli appeared as densely packed balls of collagen with no recognizable structure. Such glomeruli were often found adjacent to normal glomeruli (Figure 5A) but were also clustered in areas of dense interstitial fibrosis. The percentage of affected glomeruli varied from 20% to 90%. The severity of interstitial fibrosis also varied from patient to patient (Figure 5B). There was interstitial fibrosis in the pancreas of 4 of 5 patients (Figure 5C). Three patients had micronodular cirrhosis of the liver with severe portal fibrosis, fatty changes, and nodules of regenerative liver parenchyma (Figure 5D). Two patients had only mild portal fibrosis. Of the 4 patients with a medical history of DCM, heart sections were available from 3. We found myocardial fibrosis ranging from severe to moderate (Figure 5E). A patient who did not have a history of DCM had mild myocardial fibrosis (data not shown).

We observed testicular atrophy with obliterating fibrosis of seminiferous tubules (Figure 5F). Ovaries were densely fibrotic with cystic changes (Figure 5G). Primary or secondary follicles were absent or minimal. There was no corpora lutea. There were many hemosiderin-laden macrophages in alveoli in lungs from patients with severe myocardial and interstitial fibrosis (Figure 5H). One had a focal area of suppurative bronchitis and bronchiectasis. One lung had severe changes consistent with bronchiolitis obliterans obstructive pneumonia, including large foci of bronchial mucosa and nearly normal tissue. Relatively intact alveoli had very thickened walls and contained large macrophages, sometimes hemosiderin-laden (Figure 5I). Urinary bladders from 1 male and 2 female patients had thick foci of collagen between bundles of smooth muscle and in the submucosa (Figure 5J). There was severe reduction of cell layers in the posterior retina and nearly absent peripheral retinal cells. Deposits of melanin pigment were scattered in outer and inner nuclear layers (Figure 5K). In the few sections of brain available, no lesions were observed.

COMMENT

Alström syndrome is recognized as a complex disease that affects multiple organ systems. Diagnosis is difficult because...
Figure 5. Histopathologic findings in patients with Alström syndrome. A, Renal cortex showing small sclerotic glomeruli admixed with normal glomeruli (Masson trichrome, original magnification x50). B, Renal medulla with severe interstitial fibrosis (Masson trichrome, original magnification x25). C, Autolyzed pancreas with extensive fibrosis between lobules and around blood vessels (Masson trichrome, original magnification x50). D, Cirrhotic liver with extensive portal fibrosis and rounded regenerative nodules, 2 of which show fatty change (Masson trichrome, original magnification x50). E, Fibrotic heart with light pink–staining collagen between the cardiac muscle fibers, some of which are enlarged. Interstitial fibrosis is so mild in normal hearts that it would not show at this magnification (hematoxylin-eosin, original magnification x50). F, Testis with severely atrophic seminiferous tubules (hematoxylin-eosin, original magnification x50). G, Ovary with extensive fibrosis and devoid of oocytes, follicles, and corpora lutea. In the upper left is a portion of a cyst lined by a cuboidal epithelium (Masson trichrome, original magnification x50). H, Lung that is generally well aerated showing hemosiderin-laden macrophages (heart failure cells) in alveoli (hematoxylin-eosin, original magnification x50). I, Lung almost completely obliterated by interwoven bundles of collagen (Masson trichrome, original magnification x100). J, Urinary bladder with severe interstitial fibrosis. Normal bladders have very little collagen between smooth muscle bundles (Masson trichrome, original magnification x50). K, Severely atrophic retina showing that all layers are severely reduced in thickness from nerve fiber layer at bottom, ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform layer. The outer nuclear layer and photoreceptors are entirely lacking. A characteristic clump of melanin, presumably from the pigment epithelium, is present in the inner nuclear layer (hematoxylin-eosin, original magnification x100). All findings are from patient 30 except F (from patient 20) and I and K (from patient 137).
of the gradual unfolding of the phenotypes and the similarity to other disorders. This study reveals increasingly complex ways in which the various organ systems are involved and a more problematic clinical picture that includes features not generally thought to be associated with Alström syndrome. Pulmonary, urologic, and GI features not previously described occur in many patients. Moreover, the presence of digital anomalies and neurobehavioral involvement blurs the distinction between Bardet-Biedl and Alström syndromes.

Until now, only 1 study has suggested renal fibrotic infiltration. This study demonstrates that patients with Alström syndrome have severe fibrosis in multiple organs. This fibrosis may underlie the clinical phenotypes and suggests a common pathologic mechanism. Whether the fibrotic changes are a direct result of the mutated gene or, alternatively, an acute or late-stage chronic inflammatory response to cellular insult due to the loss of function of ALMS1 is unknown.

No clinical features were found in our patients that distinguish those with and without confirmed mutations. Research is ongoing to detect genotype-phenotype correlations and to elucidate the protein product, expression patterns, and mechanistic links to the phenotype. Intrafamilial differences in disease presentation observed in patients who carry the same mutation suggest that unknown genetic or environmental modifiers probably interact with ALMS1. Insights into the pathogenesis of Alström syndrome will depend on functional analysis of the gene. Until this information is available, a clear understanding of the broad spectrum of the phenotype, including its variability, will help resolve ambiguities concerning current diagnostic, management, and treatment strategies and minimize adverse outcomes, improve the quality of life, and lengthen the survival of patients with Alström syndrome.

Accepted for Publication: October 27, 2004.

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Funding/Support: This work was supported in part by grants from the National Institutes of Health (Bethesda, Md), the American Diabetes Association (Alexandria, Va), and the Knoll Pharmaceutical Co (North Mount Olive, NJ) (Dr Nishina); Ministero dell’Istruzione, dell’Università e della Ricerca (Rome, Italy) and Mauro Baschirotto Institute for Rare Diseases (Vicenza, Italy) (Drs Maffei and Sicolo); and grants from the Smart Family Foundation (Wilton, Conn), Stephen and Tabitha King Foundation (Bangor, Me), and March of Dimes (White Plains, NY) to Alström Syndrome International (Mount Desert, Me).

Acknowledgment: We thank the patients and their families for their participation in this study; Alström Syndrome International for continued collaboration; our many colleagues for referring and caring for the patients (Daniel Albert, MD; Cornelius Boerkool, PhD; Georges-Marie Brevière, MD; Bai-Hsiun Chen, MD; Ping-I. Chou, MD; Karine Clement, MD, PhD; Valerie Cormier-Daire, MD; Lil Falkenson, BA; Janos Feher, MD, PhD; Joseph Fisher, MD; Carl Gumbiner, MD; Jodi D. Hoffman, MD; Muriel Holder, MD; Monica Imi, MD; Margaret Klehm, CNP; Mark Korson, MD; Alex V. Levin, MD; Judith R. Mangion, MD; Claes Möller, MD, PhD; Vincenzo Munno, MD; Gabriela Porcellini, MD; G. Rassoto, MD; Ruth Riise, MD; Joanne Sutherland, MSc; Karmen Trzupek, MS; Tayfun Uçar, MD, Roberto Vettor, MD; Andrew Warren, MD; Jacques Weill, MD, R. Welsberg, MD; Steven M. Willi, MD; Melvin Yudis, MD; and Walter Zumkeller, MD); James Hannah, MD; Laurel Gray, MD; and Silke Vogelgesang, MD; for assisting with postmortem examinations and tissue preparation; Jennifer Torrance, Benjamin King, and Joyce Worcester for assisting in the preparation of figures; and Wesley C. Beamer, PhD, and Robert P. Marshall, BA, for reviewing the manuscript.

REFERENCES

Correction

Error in Figure. In the Original Investigation by Mozaffarian and colleagues titled “Fish Consumption and Stroke Risk in Elderly Individuals: The Cardiovascular Health Study,” published in the January 24, 2005, issue of the Archives (2005;165:200-206), an error occurred in the Figure on page 203, in which all except the black survival line were deleted during printing. The correct Figure appears below.

Figure. Survival free of stroke, according to tuna/other fish and fried fish/fish sandwich consumption. P=.002 and P=.02 for survival differences according to tuna/other fish (A) and fried fish/fish sandwich (B) intake, respectively (log-rank tests for equality of survivor functions).