



**5th INTERNATIONAL SCIENTIFIC CONGRESS
ALSTRÖM SYNDROME
October 17-18, 2008
Padua – Venice, Italy**



Organizing Committee: Giovanni Federspil, Pietro Maffei, Jan D. Marshall, Giovanni B. Pozzan, Cesare Scandellari, Nicola Sicolo, Roberto Vettor

Scientific Committee: Sebastian Beck, Cathy Carey, Gayle B Collin, Pietro Maffei, Jan D Marshall, Gabriella Milan, Jürgen K. Naggert, Richard Paisey, Roberto Vettor

Friday, October 17th

Padua University, Archivio Antico del Bo, Via 8 Febbraio 2, Padua

08.30 **Opening Ceremony**
Cesare Scandellari, Giovanni Federspil, Nicola Sicolo

OVERVIEW: PHYSICIAN, PARENT, AND RESEARCH PERSPECTIVES

Chairman: Phillip Beales, UK

09.00 **Childhood obesity**
Claudio Maffei, University of Verona, Italy

09.30 **Management of Pediatric Patients with Alström Syndrome**
Cristina Mihai, Spitalul Clinic de Urgenta Constanta, Romania

10.00 **New and emerging phenotypes in Alström Syndrome**
Jan D. Marshall, The Jackson Laboratory, Bar Harbor, ME USA

10.30 **The Patient & Family Perspective of Living with Alström Syndrome**
Sandra M. Hubbard-LeBlanc, Alström Syndrome International

11.00-11.30 *Coffee Break*

CLASSIFICATION AND DIAGNOSTIC ISSUES

Chairman: Jan D Marshall, USA

11.30 **The ciliopathies: a unifying genetic concept for diverse clinical phenotypes**
Nicolas Katsanis, Johns Hopkins University, USA

12.00 **Genetic testing and new diagnostic criteria of Alström Syndrome**
Sebastian Beck, Kantonsspital Münsterlingen, Switzerland

12.30 **Microarray Resequencing Chip Application for Detection of Mutations in Rare Inherited Metabolic Diseases**
R. Köksal Özgül, Hacettepe University, Ankara, Turkey

13.00-14.30 *Lunch*

DISEASE MANAGEMENT OVERVIEW AND ROUND TABLE

Chairman: Roberto Vettor, Italy

14.30 **Hormonal issues**
Pietro Maffei, Padua University, Italy

14.45 **Insulin resistance and diabetes in Alstrom syndrome**
Claudio Pagano, Padua University, Italy

15.00 **Kidney disorders**
Francesco Scolari, University of Brescia, Italy

15.15 **Cardiac consequences of Alström Syndrome: more questions than answers?**
Cathy Carey, Torbay Hospital, UK

15.30 **Heart-lung transplantation in a patient with Alström Syndrome**
Heidi Görler, Hanover Medical School, Germany

15.45 **Interactive Discussion**

16.30-17.00 *Coffee Break*

SENSORINEURAL DISORDERS

Chairman: Rod Bronson, USA

17.00 **Electrophysiology and varying degrees of visual function in different phenotypes of Alström Syndrome**
Sten Andréasson, University of Lund, Sweden

17.30 **Is epilepsy and sleep disordered breathing a contributing factor for learning disabilities in Alström Syndrome?**
Oswald Hasselmann, Ostschweizer Kinderspital, St. Gallen, Switzerland

18.00 **Understanding developmental profiles that may be present in individuals with Alström Syndrome.**
Sarah E. Shea, IWK Children's Medical Center, Dalhousie University, Canada

Saturday, October 18th

***Istituto Veneto di Scienze, Lettere ed Arti,
Palazzo Cavalli Franchetti, Campo S. Stefano 2945, Venice***

09.15-09.30 **Opening Remarks**
Caesar Scandellari, Giovanni B. Pozzan

FUNCTION OF ALMS1 and ANIMAL MODELS

Chairman: Nicolas Katsanis, USA

09.30 **Use of mouse models to elucidate ALMS1 function**
Jürgen K. Naggert, The Jackson Laboratory, USA

10.00 **Update on ALMS1 localisation and the search for binding partners**
Tom Hearn, University Southampton, UK

10.30 **Genotype-phenotype correlations in Alström Syndrome**
Gayle B. Collin, The Jackson Laboratory, USA

11.00-11.30 *Coffee break*

BASIC INVESTIGATION – SECTION 1

Chairman: Jürgen K. Naggert, USA

11.30 **Fibroblast cultures of ALMS patients: from expression profiling to functional studies**
Gabriella Milan, Padua University, Italy

12.00 **Calcium signalling and cytoskeleton abnormalities**
Rosario Rizzuto, University of Ferrara, Italy

12.30 **Identification of cytoplasmic material in ALMS neurons, and review of progress in pre-clinical studies for treatment of fibrosis in ALMS**
Roderick T. Bronson, Harvard Medical School, The Jackson Laboratory, USA

13.00 –14.30 *Lunch*

BASIC INVESTIGATION – SECTION 2

Chairman: Gayle B. Collin, USA

- 14.30 **Alms1 influences on adipose tissue. Studies in Alms1-/- mice and in 3T3-L1 cells**
Francesca Favaretto, Padua University, Italy
- 15.00 **Alström and Bardet-Biedl syndromes; common etiologies, phenotypes and shared therapeutic goals**
Phillip Beales, Institute of Child Health/Great Ormond Street Hospital for Children, UK
- 15.30-16.30 **Oral Communications**
Chairman: Sebastian Beck, Switzerland
- 16.30 **Closing remarks**
Cesare Scandellari, Giovanni Federspil, Nicola Sicolo

Childhood obesity

Claudio Maffeis

Department of Mother & Child, Biology-Genetics, Section of Pediatrics, University of Verona, Italy.

claudio.maffeis@univr.it

The reasons why a so high number of children are obese in the industrialized world are still unknown. Available data suggests that several factors contribute to excess fat mass gain in childhood. All these factors affect, directly or indirectly, energy balance equation so that energy intake is greater than energy expenditure and part of the energy ingested is accumulated in the fat tissue. The complex self-regulatory mechanisms devoted to the adjustments of food intake to energy and nutrient requirements seem to be scarcely efficient in a progressively higher number of individuals who become obese. The exposure to a so obesogenic environment make difficult to adopt adequate behaviours that protect from obesity. Individual motivation and social support are crucial especially in adolescents whereas, in the youngest, family involvement is a priority.

Consistent evidence was accumulated on the role played by diet composition, patterns of food intake, portion size. However, recent interesting observations suggest that also the intrauterine exposure to maternal over- or under-nutrition, early exposure to high protein intake as well as to formula feeding, or rapid weight gain in the first months of life are potential risk factors for obesity in children.

On the basis of its high fat oxidation rate, skeletal muscle activity is essential in fat (energy) balance equation. Therefore sedentary behaviour, associated with video exposure as well as a low level of fitness, is an important and independent risk factor of obesity. Interestingly, a low intensity exercise, as walking at the speed of 4 km/h, is able to promote the highest fat oxidation rate per min in obese children, avoiding the discomfort and the risks of performing more intense exercises. Walking is simple, cheap, safe, and strongly recommended both in the prevention and treatment of overweight in children.

Morbidity associated with childhood obesity, such as hypertension, dislipidemia, impaired glucose tolerance, and psychological disturbances, as well as tracking of obesity from childhood into adulthood are the main reasons why obesity has to be faced and treated as early as possible in childhood. Early diagnosis and care are mandatory for all paediatricians.

References

Maffeis C, et al. Insulin sensitivity is correlated with subcutaneous but not visceral body fat in overweight and obese prepubertal children. *J Clin Endocrinol Metab.* 2008;93(6):2122-8.

Maffeis C, et al. Waist-to-height ratio, a useful index to identify high metabolic risk in overweight children. *J Pediatr.* 2008;152(2):207-13.

Maffeis C, et al. Fat cell size, insulin sensitivity, and inflammation in obese children. *J Pediatr.* 2007;151(6):647-52.

Cortese S, Maffeis C, et al. The Relationship Between Body Size and Depression Symptoms in Adolescents. *J Pediatr.* 2008. [Epub ahead of print]

Management of Paediatric Patients with Alström Syndrome

Cristina Mihai

Spitalul Clinic de Urgenta Constanta, Romania

cristina2603@yahoo.com

Early management interventions are warranted in Alström syndrome patients.

Regular ophthalmologic evaluations: ophthalmologic assessment should be sought as soon as possible. No therapy for the progressive visual 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. Red-tinted prescription glasses are helpful in alleviating the distress children experience in bright lighting. Educational planning should take future blindness into consideration.

Regular testing for diabetes mellitus by fasting glucose or glucose tolerance testing.

Calculation of body mass index (BMI) and dietary evaluation is appropriate if obesity is present. To manage obesity, multiple strategies are advocated, including diet, exercise and behavioral therapies. Education and dietary measures to control weight gain education must be initiated at an early age. No formal trials of drug therapy (appetite suppressants or lipase inhibitors) have been reported. Complications of obesity, such as hypercholesterolemia and diabetes mellitus, should be treated as in the general population. Regular lipid profiling.

Occasional liver function testing to assess for hepatic failure. Aggressive treatment with variceal banding and β -blockers is warranted in patients with portal hypertension and varices

Endocrinologic testing may be necessary and includes glucose tolerance testing (GTT) for diabetes mellitus, lipid levels, and assessment of thyroid, the pituitary gland and liver functions. Thyroid function testing particularly if there is weight gain, changes in temperament and/or diminished activity. Replacement therapy with L-thyroxin and testosterone, when needed. Metformin and/or estroprogestin compounds have been employed to manage irregular menses. The full balance between risks and benefits of growth hormone replacement has not yet been proven in Alström Syndrome.

Routine (at least annual) measurement of blood pressure.

Judicious monitoring of renal function (blood chemistry initially) is warranted in all individuals. If serum concentrations of urea, creatinine, and electrolytes are abnormal, renal function scans will be planned. ACE inhibitors should be prescribed to preserve kidney function according to general guidelines.

Renal transplantation has been successful, although the immunosuppressants used following transplantation can compound the weight problem.

Cardiac evaluation should include auscultation, ECG, and echocardiography. Long-term angiotensin-converting enzyme (ACE) inhibition is indicated for the patient with cardiomyopathy.

Hearing evaluation: otoacoustic emissions and audiometry may reveal subclinical hearing loss. Conductive loss is common in children as a result of otitis media.

Developmental assessment and/or educational evaluation periodically.

Antibiotic prophylaxis for surgical and dental procedures is indicated for individuals with cardiac anomalies. Regular vaccinations.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals (<http://www.jax.org/alstrom/index.html>).

Emerging, new and borderline phenotypes of Alström Syndrome

Jan D. Marshall

The Jackson Laboratory, Bar Harbor, ME, USA

jan.marshall@jax.org

There is so far no treatment which can cure, reverse, or prevent the medical complications of Alström Syndrome. Management is dependent upon the early expectation and detection of complications which can be treated. Anticipating all of the developing clinical features and prompt intervention generally can improve the outcome of treatment.

Although Alström Syndrome is very rare, with approximately 560 individuals identified world-wide, the cardinal features are well described. However, as in many rare disorders, there is a high degree of clinical variability and many “minor” features that have not received attention in the medical literature. We suggest that it is important to recognize these atypical presentations, as their presence may cause delay in a correct diagnosis and subsequent therapeutic management.

Expanding our knowledge base to include other, infrequent phenotypes requires genetic analysis of the unusual patients as well as those who are “typical”. Unfortunately, options for genetic testing are limited and expensive; therefore *ALMS1* mutational analysis is primarily carried out on individuals who fulfill all of the diagnostic criteria. It is rare for patients with outlying or milder features to be candidates for analysis.

We report here phenotypic observations in patients carrying *ALMS1* alterations who do not present with all of the classic diagnostic criteria. Observations and documentation of some of the unusual characteristics in patients with confirmed mutations could also provide clues to the function of *ALMS1* and the important questions regarding the influence of modifier genes. Additionally, we have identified several cases with unusual genotypic results that suggest possibilities of avenues for further research. Better technology for identification of *ALMS1* mutations will enable researchers to fully understand the entire spectrum of the features of Alström Syndrome.

. Prompted by the new and borderline phenotypes observed in patients, investigations continue in cell cycle studies, craniofacial assessments, and physiological evaluations in *Alms1* mouse models.

The Patient & Family Perspective of Living with Alström Syndrome

Sandra Hubbard-LeBlanc

Outreach and Family Services Coordinator

Mother of Cheryl – 18 year old with AS

Nova Scotia, Canada

asisandra@eastlink.ca

Alström Syndrome is multi-layered. Holistically the syndrome not only affects individuals physically but also emotionally, socially and spiritually.

I will present a real-life vantage point into living with the disease; its challenges, its frustrations and what patients, parents and families are asking professionals to understand.

The ciliopathies: a unifying genetic concept for diverse clinical phenotypes

Nicolas Katsanis

Johns Hopkins University, USA

katsanis@jhmi.edu

Defects of the primary cilium and its anchoring structure, the basal body, cause a number of human genetic disorders, collectively termed ciliopathies, since they are characterized by an overlapping range of phenotypes that include retinal degeneration, polydactyly, renal and hepatic fibrosis, obesity and a complex range of cognitive and neurodevelopmental defects. Recent data have also shown that some ciliopathies overlap not only phenotypically, but also genetically by contributing epistatic alleles that can modulate the phenotypic expressivity and penetrance. As such, the primary cilium and its associated signaling represents a useful model to understand the mechanism of total mutational load in a biological system. Towards that end, we have initiated systematic sequencing and functional evaluation of mutations of ciliary genes in a range of ciliopathy phenotypes and, using a large allelic series, have constructed preliminary models of epistasis in oligogenic disorders. Such studies will ultimately empower the predictive nature of the genotype and inform clinical management and treatment.

Genetic testing and new diagnostic criteria of Alström Syndrome

Sebastian Beck¹, Robert P. Marshall², Pietro Maffei³, Jan Marshall⁴

¹Kantonsspital Münsterlingen, Switzerland, ²Alstrom Syndrome International (ASI),

³Padua University, Italy, ⁴The Jackson Laboratory, Bar Harbor, Maine, USA

beck.sebastian@gmail.com

Two copies of the *ALMS1* gene must be changed or mutated for a person to be affected with Alström Syndrome. An Alström Syndrome patient has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers). It is possible to have many different changes in this large gene, and one parent could have one particular mutation, while the other parent carries another (different) mutation. Two unaffected people (parents) who each carry one copy of the mutated *ALMS1* gene have a 25% chance with each pregnancy of having a child affected by the disorder.

ALMS1 is the only gene responsible for Alström Syndrome. So far, we know of at least 72 totally different mutations in *ALMS1*, and there are probably many more that have not yet been identified. All of the different mutations in *ALMS1* still cause the disease we know as Alström Syndrome.

Genetic Testing for Alström Syndrome is available, but whether or not testing is pursued should be based on consideration of the individual patient's circumstances and purposes. Unfortunately, there are limited circumstances where genetic testing is useful and appropriate.

Even with the existing techniques, with reasonable effort, we are still not able to detect the *ALMS1* mutations in all Alström Syndrome patients. About 60-70% of the mutations can be found in a matter of a few weeks. An additional 10-20 % may be found after extensive examination of the gene; this may often take months or even years. There are also mutations that can not be found with the current technology and therefore, unfortunately, in some Alström Syndrome patients it is not yet possible to confirm the diagnosis in a genetic laboratory.

Therefore defining the diagnosis clinically is just as important as a genetic test. Recently we established a catalogue of clinical criteria for use in clinical practice in order to establish the diagnosis of Alström Syndrome in an individual patient as early as possible.

Endocrinological issue

Pietro Maffei, Sara Romano, Gabriella Milan, Marco Rossato, Roberto Mioni, Roberto Vettor, Nicola Sicolo

Clinica Medica 3^A, University School of Medicine, Italy

pietromaffei@libero.it

Alstrom syndrome might severely affects the endocrine system and metabolism. All ALMS patients, at a certain point of their life will present, early or later, a derangement of some endocrine organs. Detection and treatment of endocrine disorders might deeply impact on quality of life and survival of ALMS patients.

Among the endocrine alterations, a number of hormonal dysfunctions have been reported so far including male hypogonadism (78%), female endocrine abnormalities (52%), hypothyroidism (17%) and growth hormone deficiency. Hormones have a fundamental role in growth and development (thyroid, GH, sex steroids, cortisol), reproduction (estrogen, testosterone, FSH, LH, prolactin, thyroid), homeostasis (thyroid, cortisol) and changes in environment (cortisol, thyroid, aldosterone, GH, prolactin, adrenaline). Considering that ALMS involves many different organ systems it is very important to dissect primary organ dysfunction, probably related to fibrosis, from secondary organ involvement which might be reversible after adequate hormonal replacement therapy.

In this presentation will be covered the following aspects (review of literature and Case Reports from the Clinic):

- 1) GH deficiency diagnosis and rGH treatment specifically considering the impact on metabolism.
- 2) Pituitary function in ALMS including anatomical findings.
- 3) Hypogonadism in males and related treatments.
- 4) Hyperandrogenism in female population: diagnosis and possible therapy.

Insulin resistance and diabetes in Alstrom syndrome.

Claudio Pagano, Sara Romano, Pietro Maffei, Nicola Sicolo, Roberto Vettor

Clinica Medica 3[^], University School of Medicine, Italy

Claudio.pagano@unipd.it

Although severe hyperinsulinaemia and insulin resistance are a hallmark of patients with Alstrom syndrome, the exact mechanisms responsible for impaired insulin action are largely unknown. Insulin resistance develops during early childhood and frequently leads to type 2 diabetes during the 2nd-3rd decade.

Obesity and central body fat distribution, that are frequent causes of type 2 diabetes in the general population, do not seem to account for insulin resistance in these patients. It has been proposed that the genetic defect of Alms gene may be involved in the aetiology of insulin resistance and type 2 diabetes. Clinical manifestation of hyperinsulinaemia/insulin resistance include marked hypertriglyceridemia, fatty liver, increased uric acid and elevated circulating fatty acids.

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) and beta cell-preserving drugs (incretins, thiazolidinediones). A pilot study suggests that treatment with metformin does not prevent diabetes in these patients, but once diabetes has established rosiglitazone+metformin might improve beta cell function and in particular first phase insulin secretion.

Pathophysiological and therapeutic issue on insulin resistance and diabetes in these patients will be discussed in details.

Microarray Resequencing Chip Application For Detection of Mutations in Rare Inherited Metabolic Diseases

Rıza Köksal Özgül^{1,2}✉

Hacettepe University, ¹Institute of Child Health, ² Faculty of Medicine, Department of Pediatrics, Metabolism and Nutrition Unit, Ankara, Turkey. ✉ rkozgul@hacettepe.edu.tr

A rare disease is generally considered when affected patients are fewer than one individual per 2000. There are as many as 5-7000 rare genetic diseases described, affecting over a million patients. Some of these are relatively frequent in the general population and others may affect only a few patients. Lack of scientific and medical knowledge for rare diseases leads affected patients to isolation and causes a significant health problem in society.

Inherited metabolic diseases in Turkey is one of major concern among rare diseases because the number and frequency of inherited metabolic diseases is high compared to other populations. Until recently there was no opportunity for genetic testing for rare inherited metabolic diseases in Turkey, and it was necessary for most of the centers to contract services from abroad or to collaborate with research institutes from abroad. Recently, we have established a biochemical genetics laboratory in the Department of Pediatrics, Metabolism and Nutrition Unit at Hacettepe University, which provides genetic mutation screening for some inherited metabolic diseases that are seen more commonly in Turkey. These include [phenylketonuria](#), galactosemia, maple syrup urine disease, propionic acidemia, hereditary fructose intolerance, tyrosinemia, methylmalonic acidemia, glutaric acidemia, fructose-1,6-bisphosphatase deficiency, and Wilson disease.

Custom resequencing microarrays has recently emerged as a novel technology for detection of sequence alterations in multiple genes in the same experiment as a highthroughput platform. In our research laboratory, we designed the first application of DNA resequencing chip for detection of disease causing mutations in multiple genes that are responsible for inherited metabolic diseases. The microarrays (Affymetrix DNA chips) contain 50 kilobases of genomic DNA sequences that covers the exonic sequences with 25 basepairs flanking intronic regions from the splice sites of *ALDOB*, *ATP7B*, *BCKDHA*, *BCKDHB*, *DBT*, *DLD*, *FAH*, *FBP1*, *GALT*, *GCDH*, *MUT*, *PAH*, *PCCA*, *PCCB* genes.

Rather than addressing some rare disorders separately, some overlapped genetic disorders or oligogenic rare disorders can be genetically screened by using one array platform. As we experienced in our study, it would be much rapid and cost effective methodology to screen large number of samples that need genetic screening for multiple genes.

Acknowledgement

This study was supported by State Planning Organisation of Turkey, Project No: DPT 2006K120640.

Alström syndrome: a rare and usually ignored cause of hereditary tubulo-interstitial nephritis

**Izzi C, #Marega A, °Maffei P, °Milan G, °Romano S, +Tardanico R, *Scolari F*

**Division and Chair of Nephrology, Montichiari Hospital and University of Brescia; #Division of Nephrology, S. Maria della Misericordia Hospital, Udine;*

°Department of Medical and Surgical Sciences, Padua University; + Department of Pathology, Spedali Civili of Brescia, Italy.

fscolar@tin.it

Alström syndrome (ALMS) is a rare unrecognized autosomal recessive disorder affecting multiple organs (OMIM 203800), characterized by sensory impairment and chronic nephropathy, symptoms shared with other genetic renal diseases affecting proteins of the primary cilium. Kidney dysfunction has been reported in 50-80% of ALMS patients and the severity of renal disease has been correlated with mutations in exon 8.

We report a detailed characterization of the clinical and pathological features of renal involvement observed in a 49-year-old woman (index case) and her 40-year old brother of non consanguineous parents with diagnosis of Alström syndrome. They both presented key features of ALMS: infant onset cone-rod dystrophy and sensorineural deafness, adult-onset dilated cardiomyopathy, hyperinsulinemia. In the index case myocardial fibrosis was demonstrated by myocardial biopsy.

The index case also suffered from bilateral subcapsular cataract, premature ovarian failure and urologic disturbances (with normal cystogram), such as difficulty initiation voiding and recurrent urinary tract infections.

The man had primary hypogonadism and subclinical hypothyroidism.

Both were of normal intelligence and without polydactyly; the final adult height was below the 5th percentile.

The renal presentation was consistent with a tubulo-interstitial disease, as suggested by the findings of defective urine-concentrating capacity, moderate polyuria, nocturia and non significant urinalysis. Both patients had mild chronic renal failure.

Renal ultrasound of the index case revealed renal asymmetry with few bilateral cortical cysts. Renal biopsy was performed which confirmed a tubulo-interstitial nephritis characterized by interstitial fibrosis, associated with a mild degree of focal glomerular sclerosis. Most glomeruli were normal. In the brother, renal ultrasound revealed normal kidneys and no cysts.

Preliminary data of the molecular analysis of exons 8, 10 and 16 (hot spots mutation regions) of ALMS1 gene revealed a heterozygous mutation in exon 8: c.1568_1569insT. The tubulo-interstitial nephritis due to ALMS is a rare disease itself and a challenging diagnosis to recognise. In order to meet this challenge, nephrologists and pathologists alike will have to maintain a high index of suspicion in patients presenting with familial tubulo-interstitial renal disease associated with retinal degeneration (usually related to nephronophthisis), sensorineural hearing loss (usually associated with collagen IV disease) and metabolic abnormalities such as hyperinsulinemia and obesity.

Cardiac consequences of Alström Syndrome: more questions than answers?

Cathy Carey,

Torbay Hospital, Torquay Devon TQ27AA, UK

cathy.carey@nhs.net

Cardiac involvement is a significant feature of the Alström phenotype, with over 60% patients affected. Heart failure is the commonest contributor to premature mortality. The clinical expression is bimodal. The majority of patients present with a fulminant cardiomyopathy in infancy, often before other manifestations of the syndrome are recognised. Unusually for a genetically determined cardiomyopathy, most infants survive the acute phase and go on to have considerable recovery of heart function. However, by adolescence around 15% of these survivors have developed a progressive cardiomyopathy. Finally, a small number of adolescents and adults with Alström, apparently unaffected in infancy, develop a progressive cardiomyopathy de novo.

There are other important circulatory features in Alström including childhood hypertension and the 'vascular paradox', namely that there is little evidence of accelerated atherosclerosis, despite a plethora of high risk factors.

Questions:

What is the cardiac pathology in childhood?
endocardial fibrosis, myocarditis?

Why does it occur and why does it improve?

Does it ever truly resolve?

Is the apparent 'recurrence' in adolescence preventable?

What is the pathology in the older patients - dilated, restrictive?

How can we deal with important interactions?

Medication - Diabetes (metformin/glitazones), Kidneys (ACEI/spiro)

Kidneys, pancreas and lungs when considering transplantation

Why do we see hypertension, even in childhood?

Can we explain the 'vascular paradox'?

We do not have answers to these questions as yet.

Our approach in England & Wales has been to establish regular specialist multidisciplinary clinics for children and adults with Alström Syndrome. This allows us to collect longitudinal follow up data and to incorporate a range of monitoring techniques. We hope this will yield fruit over the next few years.

Heart-Lung Transplantation in a 14-Year-Old Boy With Alström Syndrome

*Heidi Goerler**, *Gregor Warnecke**, *Michael Winterhalter***, *Carsten Müller****, *Manfred Ballmann****, *Armin Wessel*****, *Axel Haverich**, *Martin Strüber**, and *Andre Simon**
*Division of Cardiac, Thoracic, Transplantation and Vascular Surgery**, *Department of Anesthesiology***, *Department of Pediatric Pneumology and Neonatology****, *Dept. of Pediatric Cardiology and Intensive Care Medicine*****, *Hannover Medical School, Hannover, Germany*

Corresponding author:

Heidi Goerler, MD

Division of Cardiac, Thoracic, Transplantation and Vascular Surgery

Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany

Telephone: (++49) 511 532 2153

Fax: (++49) 511 532 5404

E-mail: goerler.adelheid@mh-hannover.de

We present a 14 year old boy who suffered from progressive biventricular cardiac failure and secondary pulmonary artery hypertension associated with the rarely seen Alström syndrome. The boy underwent successful heart-lung transplantation. We conclude from this report that heart-lung transplantation in patients with Alström syndrome is a viable therapeutic option in selected cases. Long time follow-up will provide further information about the effect of immunosuppressive therapy on renal and liver function as well as on the development of diabetes mellitus in those patients.

Electrophysiology and varying degrees of visual function in different phenotypes of Alström Syndrome

*Eva Malm , Sten Andréasson,
University of Lund, Sweden
sol.andreasson@telia.com*

Recent development of clinical electrophysiology has led to a radical improvement in understanding etiology and pathophysiology of hereditary retinal disorders as Alströms syndrome.

Five age and gender matched patients with Alström syndrome were selected from the Swedish RP-register, and four of them were returned for repeated assessment of full-field electroretinograms and some of them also ophthalmological examinations that included tests for color vision and visual fields using Goldmann perimetri.

The aim of the examination was to characterize the clinical phenotype and to study the course of disease, with an emphasis on retinal function assessed with full-field electroretinography.

The repeated full-field ERG of these patients confirmed the course of the retinal degeneration in Alström syndrome as an early cone dysfunction, prior to a subsequent rod dysfunction, but with different rates of progression.

This study could demonstrate a striking variability of the retinal function and of disease onset and severity, which has, to our knowledge, not been described previously in Alström syndrome. The visual handicap and the final visual outcome in Alström syndrome can vary considerably, which has not been fully appreciated in previous reports.

Is epilepsy and sleep disordered breathing a contributing factor for learning disabilities in Alström Syndrome ?

Dr. Oswald Hasselmann

Neuropediatric Depmt. Ostschweizer Kinderspital St. Gallen – Switzerland

oswald.hasselmann@kispisg.ch

Data concerning developmental delay and epilepsy in patients with Alström disease are sparse and at times contradictory. It is known that patients suffering under obesity have an increased rate of sleep disordered breathing which in itself is associated with the risk of poor school performance. The incidence of epilepsy is increased in syndromal diseases in which the underlying genetic defect is ubiquitously expressed not sparing the central nervous system.

Alström patients are at an increased risk for sleep disordered breathing and epilepsy and therefore prone for reduced cognitive achievements.

Polysomnographic and electroencephalographic examination of two sisters with Alström disease will be presented in the context their respective school records. The individual contribution of sleep and electroencephalographic disturbance to their cognitive achievements will be discussed. Further an expansion of the diagnostic work-up including EEG and Polysomnography will be proposed with the aim of introducing specific treatment and rehabilitation at an early stage.

Understanding developmental profiles that may be present in individuals with Alström Syndrome.

Dr. Sarah Shea

Dalhousie University, Halifax , Nova Scotia, Canada

Sarah.Shea@iwk.nshealth.ca

Goal : To improve professionals' recognition of differences in development in children and youth with Alstrom syndrome in order to promote early recognition and intervention

Objectives:

To briefly review the data available about development and behavior in individuals with Alstrom syndrome.

To discuss the impact of sensory impairment on developmental profiles in childhood.

To review key points diagnoses of relevance, including :

Autism/Autism Spectrum Disorder/Pervasive Developmental Disorder not otherwise specified.

Intellectual Disability

Language Disorder

Generalized Anxiety Disorder

Use of mouse models to elucidate ALMS1 function

Jürgen K. Naggert

The Jackson Laboratory, USA

jkn@jax.org

Cloning of the Alström syndrome gene, ALMS1, has identified the cause of the disease as a malfunction of basic cellular structures, the centrosomes and primary cilia. The challenge in a pleiotropic disease such as Alström's then becomes to identify relevant disease pathways that are impaired by the primary genetic defect and that cause the pathology in the various organ systems.

Gene expression and protein interactome analysis of ALMS1 is expected to yield clues as to what disease pathways ALMS1 may act in and which may be misregulated in our *Alms1* deficient mouse model. Such analyses may also suggest therapeutic targets to reduce organ pathology.

Update on ALMS1 localisation and the search for binding partners

Victoria J. Knorz, Tracey L. Purvis, David I. Wilson and Tom Hearn

Division of Human Genetics, University of Southampton, UK

thearn@soton.ac.uk

To better understand its function at the molecular level we are searching for proteins that interact physically with ALMS1. Yeast two-hybrid screens and co-immunoprecipitation of epitope-tagged proteins have yielded several candidates. To identify additional candidates we are developing an approach based on tandem affinity purification of protein complexes. We are also further investigating the centrosomal localisation of ALMS1 by immunofluorescence microscopy. Refining its localisation within the centrosome could aid the identification of genuine ALMS1-interactors.

Genotype-phenotype correlations in Alström Syndrome

Gayle B. Collin

The Jackson Laboratory, Bar Harbor, ME, USA

gayle.collin@jax.org

Alström syndrome (ALMS), a progressive disorder resulting in neurosensory and metabolic anomalies, is caused by recessively inherited mutations in the *ALMS1* gene. *Alms1* is a novel gene comprised of 23 exons encompassing >250 kb of genomic DNA and undergoes alternative splicing. Results from a phenotype/genotype correlation study in patients with ALMS suggest that *Alms1* splice variants may affect kidney function differentially. Three murine models for Alström syndrome have been described and all have features which recapitulate the human disease. Thus far, the mutated alleles reported in both mouse and human occur in the latter 2/3 segment of the *ALMS1* gene. To further characterize the splice variants and modifier genes, our lab has been studying several *Alms1* mouse models on various background strains. Further knowledge of *Alms1* splicing and genetic modifiers will help us better understand how gene mutations lead to the disease pathogenesis in patients with Alstrom syndrome.

Fibroblast cultures of ALMS patients: from expression profiling to functional studies

G. Milan¹, E. Zulato¹, F. Favaretto¹, S. Romano¹, S. Campanaro⁴, G.B. Collin², J.D. Marshall², B. Zavan³, G. Abatangelo³, C. Veronese¹, J.K. Naggert², P. Maffei¹, R. Vettor¹.

gabriella.milan@unipd.it

¹ Endocrine-Metabolic Laboratory, Internal Medicine 3, Department of Medical and Surgical Sciences, University of Padua, via Ospedale 105, 35128 Padua, Italy. ² The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04609, USA. ³ Department of Histology, Microbiology and Medical Biotechnology, University of Padua, via Colombo 3, 35122 Padua, Italy. ⁴ CRIBI Biotechnology Centre, Department of Biology, University of Padua, Padua.

Introduction: Alström Syndrome (ALMS) is a rare, autosomal monogenetic disease, caused by mutation in *ALMS1* (Chr 2p13), a gene ubiquitously expressed with unknown function. ALMS shows impairments at multiple organ systems, resulting in blindness, hearing impairment, childhood-onset obesity, hyperinsulinemia, insulin resistance and type 2 diabetes.

A very common feature of ALMS patients is an extensive fibrosis evident at multiple anatomical site: kidney, heart, lung, liver, pancreas, bladder, ovary and testis. This fibrotic substitution can cause specific and severe organ failure bringing often to an early death.

Aim: we established fibroblast primary cultures from dermal biopsy of 4 ALMS patients and 3 control subjects. The cells were employed to analyze the modulation in gene expression profile and changes in functional aspects related to the presence of mutated *ALMS1* transcripts.

Research design and methods: RNA deriving from 4 ALMS patients was co-hybridized with the RNA obtained from 3 healthy controls, using an oligo-spotted microarray platform. We observed the cellular shape, the mobility and the intracellular organelles of ALMS fibroblasts grown in 3D matrix scaffolds by optical and electronic microscopy (EM). We measured the cell cycle length and the susceptibility to apoptosis of ALMS fibroblasts by proliferation assays compared to normal controls. Moreover we studied cell proliferation and collagens expression modulation in response to treatment with some fibrosis inducers (TGF- β /FGFs/CTGF). Finally, we investigated the ability of ALMS and normal fibroblasts to differentiate into adipocyte-like cells when cultured in adipogenic conditions.

Results and conclusions: From about 21500 genes represented, 188 resulted as up-regulated whereas 372 were identified as down-regulated in ALMS patients. Gene function was evaluated and modulated transcripts were clustered in main categories such as "extracellular matrix component", "cell cycle", "apoptosis" and "adipogenesis". Data analysis showed an up regulation of many collagen transcripts, a down regulation of several gene involved in cell cycle control, a modulation of genes suggesting a pro-survival trend and an higher susceptibility to adipogenesis. ALMS fibroblasts cultured in 3D display a reduction in mobility and do not go through the matrix scaffold. The EM analysis shows the alteration of cytoskeleton fibers, the presence of many exocytic vesicles and glycogen granules and the tighter cell-cell junctions. The cell cycle of ALMS fibroblasts resulted longer than controls but they are still responsive to pro-fibrotic stimuli. ALMS fibroblasts express higher level of collagens mRNAs (in particular COL8A1 and COL15A1) and up-regulated COL1A1 expression upon 48 hours of TGF- β treatment. Fibroblasts from ALMS patients are able to differentiate into adipocytes (Oil O Red positive cells) with different efficiency (30-80%) while fibroblasts from healthy control are not. Finally they display an apoptosis resistance upon taspargin treatment, as assayed by dose-dependent experiments. Taken together all these results give many insights about the ALMS fibroblast phenotype and help us to understand the pathophysiology of ALMS, especially regarding the fibrosis. Microarray and functional analysis let us to speculate about new pathways where ALMS protein can be involved, suggesting its main role in the regulation of both intra and extracellular events.

Mitochondria, calcium and cell death by apoptosis or necrosis

Rizzuto, R., Pinton, P., Aguiari, P., Blom, T., Celsi, F., De Stefani, D., Fotino, C., Leo, S., Marchi, M., Rimessi, A., Romagnoli, A., Siviero, R. and Zecchini, E.

University of Ferrara, Italy

rzt@unife.it

Mitochondria rapidly accumulate Ca^{2+} through a low-affinity uptake system (the mitochondrial Ca^{2+} uniporter, MCU) because they are exposed to high $[\text{Ca}^{2+}]$ microdomains generated by the opening of ER Ca^{2+} channels. These rapid $[\text{Ca}^{2+}]$ changes stimulate Ca^{2+} -sensitive dehydrogenases of the mitochondrial matrix, and hence rapidly upregulate ATP production in stimulated cells. At the same time, Ca^{2+} sensitizes to cell death mediators acting on mitochondria, such as ceramide. In agreement with this notion, we demonstrated that Bcl-2 reduces the state of filling of ER Ca^{2+} stores, and this alteration is effective in reducing the sensitivity to various apoptotic challenges. I will here review the latest data of the lab focusing on:

1) The effect on mitochondrial Ca^{2+} homeostasis of other signalling pathways involved in autophagy and apoptosis (Akt, FHIT).

2) The signalling route that links oxidative stress to the activation of p66shc, an isoform of a growth factor adapter acting as apoptotic inducer. We demonstrated that $\text{PKC}\beta$, activated by the oxidative challenge, induces p66shc phosphorylation, with ensuing alteration of mitochondrial structure and function [1]. We also showed that this route is involved also in adipose differentiation of muscle-derived precursors, highlighting a novel process of utmost interest in pathophysiological conditions [2].

3) The molecular elements of the mitochondria-ER Ca^{2+} connection. I will discuss the role of VDAC in rapidly channelling Ca^{2+} through the mitochondrial outer membrane and the specific functions of the various VDAC isoforms in autophagy and apoptosis.

[1] Pinton et al., *Science* (2007) 315, 659-663.

[2] Aguiari et al. *Proc. Natl. Acad. Sci. USA* (2008), 1226-31.

Identification of cytoplasmic material in ALMS neurons, and review of progress in pre-clinical studies for treatment of fibrosis in ALMS

Rod Bronson

Harvard Medical School, The Jackson Laboratory, USA

roderick_bronson@hms.harvard.edu

There has been a small amount of progress in three areas of research on Alstrom syndrome. First, it is now quite clear that the cytoplasmic neuronal material in ALMS patients, which stains with periodic acid Schiff, is not unique to ALMS but, rather, is age-related ceroid-lipofuscin. The fact that the material is so extensive even in young ALMS patients may suggest that ALMS patients' brains are aging more rapidly than non-ALMS patients. However, this could only be proven by comparing ALMS brains with brains from age-matched, chronically ill, non-ALMS patients. Second, mouse models of ALMS have been shown to develop a mild degree of fibrosis in liver, particularly if fed a high fat diet. This fibrosis does not occur in wild type mice fed a similar diet. While this fibrosis is not nearly as severe as the frank cirrhosis so common in human ALMS, it is a phenotype that can be added to the other phenotypes common to mice and people with ALMS. These include obesity, metabolic syndrome, retinal degeneration and deafness. Third, this fibrosis phenotype could be an end point in testing the efficacy of drugs designed to suppress cirrhosis, myocardial fibrosis and glomerular fibrosis in ALMS. Many anti-fibrosis drugs are presently being tested to suppress fibrosis in rat models of cirrhosis, hypertension with myocardial fibrosis and diabetic nephropathy with glomerulosclerosis. Some of these models are of questionable validity. Pre-clinical trials of such anti-fibrosis drugs as losartan, fenofibrate, polaprezinc and tetrahydrocannabinol shows that sometimes these drugs have statistically significant but relatively mild success in moderating fibrosis in heart, liver and kidney in rodent models.

Alms1 influences on adipose tissue. Studies in *Alms1*^{-/-} mice and in 3T3-L1 cells.

*F. Favaretto*¹, *G. Milan*¹, *S. Romano*¹, *C. Veronese*¹, *E. Zulato*¹, *C. Centobene*¹, *G.B. Collin*², *J.D. Marshall*², *J.K. Nagger*², *P. Maffei*¹, *R. Vettor*¹.

¹ Endocrine-Metabolic Laboratory, Internal Medicine 3, Department of Medical and Surgical Sciences, University of Padua, via Ospedale 105, 35128 Padua, Italy.

² The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04609, USA.

francesca.favaretto@unipd.it

Alström Syndrome is a rare, recessive monogenic disease with an array of clinical manifestations at multiple organs. Previously, the gene responsible for Alström syndrome (ALMS1) was identified and its translated product shown to localize to centrosomes and basal bodies of ciliated cells. Although ALMS1 has been implicated in ciliary function and intracellular transport, the biological link between lack of ALMS1 and the development of metabolic complications is poorly understood.

Several Alström (*Alms1*) mouse models have been established to gain a better understanding of the protein's function. All *Alms1* mouse models show many of the human complications of the syndrome. For example, *Alms1*-deficient mice develop retinal degeneration, hearing impairment, kidney failure, testicular atrophy and metabolic alterations such as obesity and insulin resistance. In our study, we used the *Alms*^{GT(pGT1Lxf)/Pjn} (*Alms1*^{-/-}, *Collin et al*, *Hum Mol Genet.* 2005) mouse model to investigate the role of *Alms1* in adipose tissue. This model was obtained by a gene trap cassette insertion downstream exon 13 of *Alms1*. *Alms1*^{-/-} mice are obese and males develop type 2 diabetes; insulin resistance and increased body weight became apparent between 8-12 weeks of age, with manifesting hyperglycemia at 16 weeks. In the *Alms1*^{-/-} mouse model, we examined components of the Glut4 trafficking pathway. In particular, we collected both subcutaneous and visceral adipose tissue samples from *Alms1*^{-/-} and control mice and we analyzed by qPCR *Glut4*, *InsR* and *Leptin* mRNA expression. Glut4 total protein and its translocation to the plasma-membrane were evaluated by western blot upon insulin stimulation. In addition, adipocyte primary cultures were established from subcutaneous adipose tissue and insulin sensitivity was investigated in pre-adipocytes and *in vitro* differentiated mature adipocytes. *Alms1*^{-/-} mice appear to have reduced *Glut4* and elevated *Leptin* expression when compared to littermate controls. Upon insulin stimulation in *Alms1*^{-/-} mice, Glut4 was able to move to the plasma-membrane, however we observed the reduction of total protein content compared to controls.

We also studied *Alms1* gene expression in the 3T3-L1 cell line. 3T3-L1 is a murine cell line able to differentiate from fibroblast like cells to mature adipocytes under adipogenic conditions, filling their cytoplasm with lipid droplets and increasing expression of adipose-specific genes. This cellular model is widely used to study both transcriptional and functional mechanisms driving and controlling adipogenesis. We quantified by qPCR *Alms1* mRNA content in pre-adipocytes and during differentiation with and without thiazolidinediones or insulin treatment. In addition, we investigated whether *Alms1* transcription can be modulated by insulin sensitivity, by measuring its expression in pre-adipocytes and adipocytes after acute or chronic treatments with rosiglitazone and insulin, which are known to modify insulin sensitivity. In 3T3-L1 we observed a decrease in *Alms1* expression during adipogenic differentiation. However, when adipogenic drugs were acutely applied to pre-adipocytes or fully differentiated adipocytes *Alms1* expression remained the same.

In conclusion our data suggest a role of *Alms1* in proliferation/differentiation of adipose cells and in the Glut4 pathway. Elucidating the interacting components of *Alms1* in both events may give us a better understanding of how *Alms1*-disruption could lead to the development of obesity and diabetes.

Alström and Bardet-Biedl syndromes; common etiologies, phenotypes and shared therapeutic goals.

Phil Beales

Institute of Child Health/Great Ormond Street Hospital for Children, UK

p.beales@ucl.ac.uk

Bardet-Biedl syndrome (BBS) has many similarities with Alström syndrome (AS). Patients develop progressive visual loss owing to retinitis pigmentosa, weight gain escalates soon after birth, many patients have developmental delay and experience educational difficulties. They can also develop renal cysts which can progress to renal failure. Unlike Alström syndrome, most are born with extra digits.

There is widespread heterogeneity in BBS with around 15 responsible genes which when mutated cause disease. By contrast, AS has a single responsible gene association, *ALMS1*. Most BBS proteins, like *ALMS1* localise to the centrosome and basal body. In this talk I will compare and contrast the syndrome phenotypes, review the related genetics and biology and discuss some of our recent work revealing connections to AS and possible therapeutic interventions.

Microperimetry and OCT findings in a new case of Alström Syndrome

S. Salvatore, S. Cavarretta MD*, S. Lupo MD*, PL Grenga MD*, P. Maffei[°] MD, G. Milan[°] MD, EM Vingolo, PhD**

***“La Sapienza” University of Rome, Department of Ophthalmology, Alfredo Fiorini Hospital, Terracina, Italy*

[°] Department of Medical and Surgical Sciences, University of Padua, Padua, Italy

serena.sal@hotmail.it

Purpose:

To study by means of optical coherence tomography (OCT) and MP-1 microperimetry a new case of Alstrom Syndrome (AS).

Materials and Methods:

A 5 year old boy with a genetically confirmed diagnosis (homozygotic mutation: 8938C>T - Gln2980TER on exon 10) underwent a complete ophthalmological examination.

Results:

BCVA was 0.3 in both eyes. Slitlamp biomicroscopy unremarkable. Fundoscopy revealed pale optic disc, optic nerve head drusen, cone-rod retinal dystrophy, attenuated retinal vessels, salt and pepper peripheral lesions in both eyes. The ERG showed no recordable response. VEP were reduced in both eyes.

MP-1 microperimetry (Nidek Technologies, Italy) disclosed an infero- nasal absolute scotoma in the right eye (RE) and absolute para-central scotomas in the infero-nasal and supero- temporal field in the left eye (LE); fixation relative unstable in both eyes, since 43% of the fixation points were inside the 2 degree diameter circle and 77% were inside the 4degree diameter circle in RE, and 40% of the fixation points were inside the 2 degree diameter circle and 79% were inside the 4 degree diameter circle in the LE. Mean retinal sensitivity was reduced in both eyes: 11,8 dB in RE and 11,6 in LE.

OCT: Retinal thickness/volume analysis demonstrated a slightly reduced thickness over all the central retina in both eyes. The retinal layers were scarcely visible particularly the photoreceptors layer.

Comment:

Pigmentary degenerations of early childhood are present in a large number of inherited syndromes. In such patients, other systemic manifestations may be difficult to evaluate or may not become apparent until adulthood.

This is the first time that microperimetry and OCT findings are described in a case of AS. Microperimetry allows a detailed and precise, point to point correspondence between the fundus image and the perimetric results of the vision- threatening macular changes associated with this disease that cannot be obtained by means of projection perimetry. MP-1 biofeedback examination may be used as a basis for future rehabilitation, thus the follow-up of these findings could bring a useful support to these patients and provide useful insight into the diagnosis, especially when the clinical criteria are unclear.

Case report: Atypical phenotype in Alström Syndrome associated with major heart and lung derangements and mild retinopathy

S Romano, JD Marshall, F Calabrese**, F Braccioni***, U Fantoni***, G Milan, GB Collin*, G Pozzan****, JK Naggert*, N Sicolo and P Maffei*

*Dept. of Medical and Surgical Sciences, Dept. of Diagnostic Medical Sciences and Special Therapies**, Dept. of Cardio-Thoracic Sciences*** of Padua University, Italy; The Jackson Laboratory*, Bar Harbor, US; Dept. Of Pediatrics****, Venice-Mestre Hospital, Italy.*

saroma79@hotmail.com

Alström Syndrome (ALMS) is a rare autosomal recessive genetic disease caused by mutations in *ALMS1*. Atypical clinical presentations and phenotypes offer the unique possibility to shed new light on *ALMS1* gene function. Mutations of exon 8 appear to be associated with less severe nephropathy than is seen in patients with mutations in exon 16.

We report on a 20-year-old boy with two confirmed *ALMS1* heterozygous mutations (exon 12, c.9901_9902insC and exon 10, c.8782C>T). This patient was obese and had sensorineural hearing loss, retinal degeneration and heart-lung impairment since childhood. However, unlike most other reported cases that “define” the Alström Syndrome phenotype, this patient maintained good residual visual acuity and presented normal height (75th centile) with long extremities. Consistent with the accepted ALMS phenotype, his external genitalia were underdeveloped. He has biventricular cardiac failure and dilated cardiomyopathy, wide endomyocardial and ensocardial fibrosis, moderate mitral valve insufficiency and secondary pulmonary artery hypertension, diagnosed in early infancy. Since the age of 16 he has presented frequent pulmonary infections. Bilateral bronchiectasis were eventually discovered and a diagnosis of restrictive ventilatory defect was made.

At the age of 20 he was hospitalized for dyspnea, bronchial hypersecretion, atrial fibrillation and heart failure with low ejection fraction. Regarding the arrhythmia, the patient obtained a spontaneous restoration of sinus rhythm and stabilization of hemodynamic parameters. A CT scan of the chest showed mild bilateral pleural shedding, interstitial fibrosis and bulky bilateral hilar and mediastinal lymphadenopathy. Lung involvement was also investigated by bronchoscopy, transbronchial lung biopsy and BAL. The laboratory investigation of immunity system was uneventful (peripheral + BAL). A lung CT-PET scan excluded tumor involvement and bronchial endoscopy disclosed widespread reddening of the bronchial mucosa. Further histological evaluation showed marked fibrous interstitial thickening of the lung with mild lymphocytic and monocytic infiltration. Extensive microbiological investigations of bronchial fluid by means of PCR revealed *Aspergillus* and Parainfluenza type 3 virus. Tuberculosis was excluded by specific microbiological testing. *Aspergillus* infection was treated without resolution of lung lymphadenopathy. Pulmonary function testing showed a restrictive ventilatory defect with a moderate reduction of carbon monoxide diffusion capacity and blood gas analysis was normal. A cardiopulmonary exercise testing was consistent with a severe exercise intolerance showing a VO₂ peak of 10.8 mL/Kg/min (22% pred) reached at a work rate of 38 watts (14% pred).

In conclusion, this case confirms the wide clinical heterogeneity of ALMS patients. It could be observed that unusually mild retinopathy might be associated with major derangements of heart and lung function. Pulmonary histological investigation confirmed that tissue fibrosis remains a typical anatomical finding. Mediastinic lymphadenopathy might be considered a new aspect associated with chronic lung infections in ALMS.

GENETIC DIAGNOSIS OF ALSTRÖM SYNDROME: Padua Hospital experience in 2006-2008.

Zulato E, Centobene C, Veronese C, Romano S, Granzotto M, Favaretto F, Sicolo N, Vettor R, Maffei P., Milan G.

Endocrine – Metabolic Laboratory, Department of Medical and Surgical Sciences, University of Padua, Italy

elisabetta.zulato@unipd.it

Introduction. Alström Syndrome (ALMS) is a recessively inherited disorder with a complex and variable clinical spectrum. ALMS is caused by mutations in the *ALMS1* gene, located on chromosome 2p13. *ALMS1* is ubiquitously expressed and codes for a protein of unknown function. Several disease-causing variants have been identified, primarily clustered in exons 8, 10 and 16. The majority of mutations are nonsense and frameshift variations (insertions or deletions) that are predicted to cause premature stop codon. **Aim.** The role of genetic testing in ALMS individuals and families is still under debate. Since 2006 this Hospital has offered the possibility to search for *ALMS1* mutations under the full coverage of National Health Service. We evaluated the impact and usefulness of this service on population as well as the medical community. **Research design and methods.** We set up a test based on direct *ALMS1* gene sequencing for cases referred with a high clinical suspicion (retinopathy in all cases). First, we analyzed exons 8, 10 and 16 by PCR amplification of gDNA obtained from peripheral blood samples and sequenced with ABI 3100 Sequencing Analyzer. As a second line of analysis, we sequenced cDNA obtained from patients' dermal fibroblasts. The latter test allowed us to amplify and sequence all the ORF with fewer reactions, reducing costs and execution time of the genetic investigation. The latter was performed only in some patients, when we failed to identify *ALMS1* mutations in exons 8, 10 and 16. **Results.** In 2006-2008 we studied 23 Italians and 1 European subject. Fifty two percent of these individuals were followed at Padua Hospital while 48% were referred from other centers. The majority of the genetic testing was done using gDNA (83%) and only 3 from fibroblasts cDNA (17%). Most (79%) of the requests for genetic testing resulted from a clinical diagnosis of ALMS, 16% were from non-affected individuals (relatives), and particularly in case of pregnancy (3 cases) or post-mortem investigation (1 case). Two patients had been previously diagnosed on a research basis (Jackson Laboratory, Bar Harbor, USA) and needed confirmation of the results for legal reasons. We found mutations in 16/21 subjects with a clinical suspicion of ALMS (76%); no mutations were identified in only 5 subjects (24%). In 13/16 subjects we completely described the genotype, while in 3/16 subjects mutations were detected only in one allele. Finally, we identified 5 novel disease-causing variants with a deletion or insertion in exons 8 and 16 and a nonsense mutation in exon 10. **Conclusion.** The combination of typical signs and symptoms with a first-line genetic investigation of exons 8-10-16 seems to reach a conclusive ALMS diagnosis in almost 80% of cases. However, the availability of genetic testing opens new questions including pregnancy counseling, legal issues and non-affected carriers doubts.

Some Metabolic Aspects of Alström Syndrome

Dr Cathy Carey,

Torbay Hospital, Devon, UK

On behalf of

Dr Richard Paisey & Professor Tim Barrett lead clinicians and their teams, Alström Syndrome Specialist service, National Commissioning Group, National Health Service, England and in association with AS UK and AS International

Insulin resistance and central obesity are cardinal features of Alström syndrome, and are often associated with hyperglycaemia and hypertriglyceridaemia. While there are similarities between Alström and classical metabolic syndrome/Type 2 diabetes, intriguing differences are emerging.

1. Response to high protein/fat and high carbohydrate meals

Metabolic measures in patients with Alström Syndrome taken after equicaloric high fat and high carbohydrate meals showed no changes in serum glucose, insulin or triglycerides after the high fat meal. However, although triglycerides remained stable after the high carbohydrate meal, glucose and log insulin levels increased. This study suggests that low carbohydrate advice may prove more effective than fat restriction in control of hyperglycaemia and hyperinsulinaemia.

2. Fat Distribution

In metabolic syndrome, central adiposity is accompanied by a visceral preponderance of fat. However, while obesity is also typically central in Alström syndrome, CT/MRI imaging studies show a striking subcutaneous distribution of fat.

3. Absence of clinical peripheral neuropathy in diabetes associated with Alström Syndrome

Peripheral sensor-motor neuropathy is a common complication of type 2 diabetes. In a large clinical testing study in Alström syndrome, there was striking full preservation of protective foot sensation. In contrast, a significant number of young onset type 2 diabetic subjects had early neuropathy. This study reassures Alström families that exercise can be undertaken without risk of foot ulceration. Further studies may provide a clue to the causes of differential susceptibility to neuropathy in the wider diabetic population.

4. Encouraging early experience with exenatide

Exenatide is an incretin mimetic, an injectable analogue of glucagon-like peptide 1 (GLP-1). Six month experience in adults with Alström is promising, with clinically significant reductions in weight and glycosylated haemoglobin.

Patient-Led Structured Specialist Services: A personal perspective on the evolution of care for Alström Syndrome in England

Cathy Carey

Torbay Hospital, Devon, UK

In 1997, I was one of several doctors invited to the first family conference held by Alström Syndrome UK (ASUK). My invitation was because I was the cardiologist for one of the conference participants. At the time, worldwide experience with Alström was tiny - Jan Marshall had identified around 45 patients between the medical literature and personal contacts.

The meeting is still vivid in my mind. I began to understand how challenging this condition is to live with, an uphill struggle for patients and their families. I also heard of much unhappiness with medical professionals due to factors such as delayed diagnosis, multiple hospital visits, multiple specialists and life-long struggles with health. Similar problems related to education. Patients and families felt they were fighting a battle on many fronts. Finally I began to understand that the clinical features of the syndrome are cumulative, distressing, and potentially life-threatening at any age, diverse and often difficult to manage.

Initially, as medical professionals, we provided an informal 'ear' to help families who wanted to understand the complexities of the medical issues. At the request of patients and ASUK, this developed into a more structured yet unrecognised clinical service and was combined with joint research and data collection. Parallel with this, the support group found they were regularly dealing with a range of social and educational concerns requiring increasing time and input which could not be sustained on a voluntary basis.

In England, the National Commissioning Group of the NHS handles medical conditions where patient numbers are small, but needs are very costly or specialised, such as gene replacement therapy for glycogen storage disease. Annual reports and detailed review of the service are mandatory. AS UK, in partnership with Torbay Hospital (adults) and Birmingham Children's Hospital (paediatric) successfully lobbied for a funded, nationally recognised specialist Alström Syndrome service, which began in 2006.

Firstly, the service provides regular clinical assessments with specialists experienced in Alström syndrome at a single, tailored hospital visit (includes diabetes, endocrine, cardiology, respiratory, audiology, dietetics, psychology etc.).

The unique part of the Alström programme is the central involvement of the patient support group, with opportunity for patients and families to meet each other informally and learn from each other, as well as updates about diet, exercise, relevant social services, financial benefits and education. For patients who do not want to travel, advice is readily available for their clinicians.

In summary, this patient-led clinic format has evolved over a decade and endeavours to encompass specialist medical, social and self care needs of patients with Alström Syndrome. This format may provide a prototype for managing other complex rare disorders.

With thanks to AS UK and all involved in the Alström Syndrome Specialist service, England.