

AS Research for AS UK

The raison d'être is to define phenotype and explore best treatments for each of the complications of AS in order to improve quality of life and longevity in persons with the syndrome.

It is appropriate to consider the researches so far brought to fruition and planned for the future under the sub divisions of complications.

Genetic Basis of the Condition

The ALMS 1 gene has been identified simultaneously by two groups independently. Following this finding AS UK has funded an interim genetic analysis in 12 phenotype AS British subjects. It is notable that most of the known 200 + phenotypic AS subjects worldwide have not been genotyped. This circumscribed project has shown a possible UK founder effect and allows an early assessment of the involvement of "mild" Alström gene changes in type 2 diabetes or cardiomyopathy. Genetic test to confirm diagnosis and allow genetic counselling has therefore become more feasible.

Blindness

Early cone rod dystrophy has profound implications for AS children. So far early introduction of Braille whilst utilising residual vision maximally and provision of guide dogs and buddies where appropriate to facilitate access to education and work are helpful, and could be studied/audited.

In the future the identification of the gene opens up the prospect of detecting more mild cases of AS without visual loss if they exist, and tracing the causes of visual loss from study of the Alström protein encoded by the gene.

Hearing Loss

Early detection of nerve deafness and provision of good digital hearing aids is essential, as is exclusion of superadded conduction deafness and its treatment.

In the future it may be that particular mutations of the ALMS 1 or other genes in phenotypically Alström subjects may be found to be specifically linked to inner ear function.

Hyperlipidaemia

We have assessed frequency and severity of hypertriglyceridaemia in Alström Syndrome and its relationship to insulin resistance (ref.). We are preparing a further manuscript on glucose, insulin and triglyceride responses to meals coupled with most effective treatment of acute and chronic hypertriglyceridaemia.

Insulin Resistance and Type 2 Diabetes

Virtually all phenotypically Alström persons have insulin resistance, sometimes with acanthosis nigricans and high body fat (approx 40%), and a high prevalence (>50%) of progression to diabetes mellitus by the teenage years. We have contributed to an overview article of 130 patients in press Archive Int Med. Further UK studies have suggested that the obesity may be of unusual distribution with mainly subcutaneous not visceral fat deposit. Diabetes responds to metformin, calorie and CHO restriction and can progress to insulin requirement.

A number of Alström teenagers commenced on insulin are not helped by it and can withdraw the injections, relying on metformin and lower carbohydrate and fat intake. A systematic review of energy intake is also being undertaken to throw more light on the possibility that the syndrome is associated with a low metabolic rate.

Neuropathy

Feet There are compelling reasons to encourage independence in daily life and exercise in those with Alström Syndrome. However the frequent co existence of type 2 diabetes, often with sub-optimal glycaemic control gives rise to concerns about foot problems due to diabetic neuropathy. If this were to occur AS persons would be at greater risk of ulceration because of the reduced vision. In view of these concerns the AS UK team has joined with AS international to systematically review neurological foot examination and symptom questionnaire in 40 Alström subjects, 34 with type 2 diabetes.

The questionnaire elicited no symptoms related to neuropathy such as tingling or burning at night. The examination revealed good skin nutrition, and 100% sensitivity to graded monofilament and vibration sensory testing. This is an excellent result in that neither the syndrome as such or associated diabetes resulted in neuropathy in this group. For comparison, in 100 new adult type 2 diabetic subjects >40% were insensate to at least one of the 4g monofilament test sites. Although the Alström subjects were younger (5-35 years) some had experienced 15-20 years diabetes with HbA_{1c} > 9%.

In patients so far studied it was possible therefore to strongly recommend full social and educational activities with regular walks, swimming etc. without concern that there would be an undue risk of foot ulceration.

The Heart The high incidence of both infantile and adolescent cardiomyopathy is of greatest concern to Alström families. The fact that sometime intractable cardiomyopathy occurs in a syndrome also characterised by insulin resistance and diabetes could indicate an underlying cause for the heart failure in increased arterial stiffness. Conversely, autopsy studies have shown widespread tissue fibrosis in the condition so that there may be a primary myocardial problem, or both these factors may operate. Furthermore anecdotal evidence suggests that early detection and treatment of heart failure in the syndrome can much improve quality of life. In this respect, renewed interest in early detection of heart failure from serum levels of brain natriuretic peptide is relevant. To this end we have obtained ethics committee permission to examine augmentation index and pulse wave velocity by radial artery doppler, coupling this with echocardiogram and serum insulin. The tests will be performed on 17 young persons with Alström Syndrome in October 2004. There is a possibility that the AS gene may sometimes result in cardiac problems without other manifestations this can now be explored.

The Bladder and Urinary Tract The largest survey of AS persons has shown a 20% prevalence of urinary symptoms best categorised as detrusor urethral dyssynergia. The painful spasm may be helped by antispasmodics, but once retention of urine occurs intermittent self-catheterisation or in one case urinary diversion with an ileal bladder can be required. These problems do not seem to be linked with the renal impairment that can occur as this occurs independently of bladder problems and is accompanied by renal fibrosis.

Bowel Problems As with the urinary tract, dysmotility of the oesophagus is common in Alström Syndrome, and associates with severe acid reflux. Weight control, reduced CHO diet, protein pump inhibitors and raft therapy, as well as cisapride can help.

Conclusion

We hope to improve the quality and length of life of those with Alström Syndrome.

1. By identifying the most effective treatments for overweight, insulin resistance, diabetes and hyperlipidaemia.
2. Through evaluating the pathways to causation of cardiomyopathy and refining treatment.
3. Exploring the genetic basis for condition and links between particular mutations or modifier genes and phenotype.
4. Recommending best practice for annual review of AS patients.
5. Promoting early introduction of Braille, digital hearing aids and mobility support for independent living and safe exercise.