

## **Guidelines and rationale for treatment of endocrinological disorders and diabetes occurring in the Alström syndrome**

1 ) Insulin resistance 2) Diabetes mellitus 3) Endocrine - pituitary, thyroid, gonadal, growth hormone 4) Lipids

### 1 ) Insulin resistance

Insulin is the hormone which channels sugar into cells and increases the enzyme systems which store sugar as glycogen in muscle and liver. It also promotes storage of fat and building up of proteins including muscle in the body. Any condition which results in abdominal obesity will result in a resistance to the actions of insulin and increased levels of this hormone. This so-called insulin resistance syndrome is often associated with high blood fat levels, high blood pressure and a dark pigmentation of skin flexures. This darkening of skin is called acanthosis nigricans and is not in itself in any way harmful.

### 2) Type 2 diabetes mellitus

In the presence of insulin resistance, diabetes, characterized by a fasting blood glucose greater than 7 mmol/l, will develop in those who have an inherent weakness of insulin secretion from the cells of the pancreas. Many, but not all, Alström syndrome persons develop diabetes mellitus in their early teens.

Studies of overweight adults with type 2 diabetes have shown that weight reduction of 10 kg and aerobic exercise equivalent to 3 hours' brisk walking per week can improve control of diabetes as well as many other aspects of cardiovascular health.

In addition, an established tablet treatment - Metformin, is known to reduce average blood glucose levels and complications of diabetes affecting the heart, kidneys and nervous system.

The aim of such treatments is to ensure that an Alström syndrome patient is enabled to be enjoyably physically active, to benefit from a healthy diet and, if diabetic, to aim for glycosylated haemoglobin (HbA1c) levels of 6% (upper limit of non-diabetic population).

### 3 High blood fats - hyperlipidaemia

Insulin effectiveness is crucial in facilitating flow of excess fatty acids and sugars into fat cells as storage (3,500 kcal per lb of fat!) Like many overweight type 2 diabetic persons, those with Alström syndrome and diabetes can have potentially harmfully increased levels of blood triglycerides. These can sometimes be normalized by diet, exercise and Metformin, but if not, may be reduced by treatment with well-established tablets such as the statins or fibrates. However, those with serum triglyceride levels >10mmol/l are at risk of pancreatitis, and respond best to treatment with Niaspan, 3 grams daily at night (a form of nicotinic acid). Very little data exists however about the safety and efficacy of such treatments before puberty.

### 4 Endocrine disturbances

The pituitary gland at the base of the brain has been likened to the "conductor of the orchestra" as it releases stimulating hormones which control secretions of the thyroid, adrenal glands, ovaries and testes. In addition, the pituitary gland releases growth hormone which directly affects metabolism and indirectly causes growth in childhood, as well as prolactin, the milk hormone.

If hormone deficiencies result from pituitary underactivity, these are called "secondary", but if they result from failure of one of the glands, "primary".

A whole range of hormone deficiencies has been described in some young people with the Alström syndrome:

a) Primary hypothyroidism An underactive thyroid gland successfully responding to treatment with thyroxine tablets.

b) Primary hypogonadism

In the male this results in low levels of testosterone, reduced bone and muscle strength (long term) and lack of sexual development or potency. This is successfully treated with weekly or twice monthly injections of testosterone from puberty onwards.

In the female failure of periods and reduced sexual development/arousal result. Treatment with cyclical oestrogen and progesterone is important and effective.

c) Secondary hypogonadism

When the pituitary fails to stimulate the ovaries or testes, then hypogonadism results in the same way as in primary failure of the ovary or testis and treatment is the same.

d) Growth and development

Growth in height stops soon after the pubertal growth spurt. There is some evidence that this may occur early in some Alström cases, which would reduce final height attained. Such premature puberty can be delayed in either sex, but this has not yet been tried in the Alström syndrome.

Short stature can also result from failure of growth hormone secretion from the pituitary. Careful testing is necessary to establish that growth hormone deficiency is present in a child: treatment by growth hormone injection can help but must be closely monitored.

Growth hormone replacement in deficient adults is the subject of intense controversy. If present in the Alström syndrome, strength of the heart muscle might be affected in those with adolescent cardiomyopathy but much more work is required to establish this.

### Hormone and metabolic interactions

The effects of diabetes, disturbed blood fats and hormone deficiencies overlap and interact. It is important to state that treatment of diabetes as outlined above, of high blood fats and hormone replacement therapy can all be given in conjunction with one another safely and to good effect. This also applies to superadded treatment for hypertension and heart failure.

### Monitoring

It would be reasonable to suggest a single fasting blood sample annually which should be **tested for:**

#### Aim

fasting blood glucose	under 7 mmol/l
fasting cholesterol	under 5 mmol/l
fasting triglycerides	under 2 mmol/l

glycosylated haemoglobin (HbA1c) under 6 mmol/l

thyroid stimulating hormone 0.5 - 5 mU/l free thyroxine check local laboratory serum testosterone 8 - 40 nmol/l (male only)

as well as kidney and liver function