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Wolfram syndrome guide for endocrinologists

Apart from diabetes mellitus, other common endocrine findings in Wolfram syndrome include:

Diabetes insipidus.
Diabetes insipidus of central origin occurred in 72% with a median age of onset of 15.5 years (Barrett et al 1995). The range in age of onset is broad, possibly because of delays in establishing the correct diagnosis. Common symptoms include polyuria and polydipsia; the differential diagnosis includes polyuria secondary to poor glycemic control, and neuropathic bladder.

Useful investigations include 24 hour urine collection to assess volume, particularly if the patient denies symptoms. To make the diagnosis of cranial diabetes insipidus, an assessment of the concentrating ability of the urine is required. It is easiest to collect morning paired fasting urine and fasting plasma for osmolarity and sodium concentration. Water deprivation tests are best avoided as they can be dangerous. A urine osmolarity > 500mOsmol/L with normal serum sodium (up to 145mmol/L) and serum osmolarity (up to 295mOsmol/L) in the presence of normal serum glucose effectively excludes diabetes insipidus. A confirmation of diabetes insipidus would by a urine osmolarity <150mOsmol/L, with serum Na > 145, and serum osmo > 295mOsmol/L.

Management is with desmopressin replacement according to local practices. The options are usually intranasal, buccal or oral. The intranasal preparations are about 20 times more potent than the oral, and about 15 times more potent than the buccal preparations. A safe starting dose in a child over 5 years would be 2.5 micrograms intranasal at night; and for an adult, 5-10 micrograms intranasal. The dose needs to be titrated according to symptoms, and by blood and urine biochemistry. As with diagnosis optimising management can be difficult due to polyuria secondary to poor glycemic control, and neuropathic bladder.

Hypogonadism.
Hypogonadism is more prevalent in males than in females. It can be either hypogonodatrophic (i.e., central) or hypergonadotrophic (i.e., secondary to gonadal failure). The underlying pathology of either type is not understood. Females usually retain their ability to become pregnant; about six successful pregnancies are described in the literature. One female had absence of the uterus [Tranebjærg, unpublished].

Symptoms to enquire about include for children, delayed puberty (the absence of secondary sexual characteristics by 14 years in a girl or 16 years in a boy), pubertal arrest. In adult men, ask about erectile impotence, reduced libido, and any history of impaired fertility or oligo/azoospermia. On examination, small, soft testes have been reported. For women, ask about amenorrhoea or oligomenorrhea, infertility loss of libido, and dyspareunia. Helpful investigations include assessment of sex hormone levels (testosterone and SHBG (or oestradiol), FSH and LH, and inhibin B in males. Management involves hormone replacement in the standard way (*i.e* testosterone substitution in male patients, estradiol-progestagen (HRT) substitution in female patients).

Hypothyroidism
The frequency of thyroid dysfunction in Wolfram syndrome is not known. It is prudent to include an assessment of TSH in annual review investigations; and in the presence of symptoms, to measure free-T3, free-T4 and TSH. Thyroid substitution therapy can be given if required with L-Thyroxine (starting dose 25micrograms/day in children, 50 micrograms/day in adults)

Growth retardation. Most adults have normal height, but growth retardation is not infrequent. This may relate to pubertal disturbance in those with hypogonadism. Linear growth should be monitored in children using standard growth charts.