Birmingham Children's Hospital NHS
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Growth and endocrinopathy in Wolfram Syndrome: the experience of a nationally commissioned specialist service

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Introduction

Wolfram syndrome (WS) is a rare genetic disorder, with autosomal dominant inheritance, secondary to a mutation in the Wolframin gene (WFS1) on chromosome 4p. The condition is rare with a prevalence of 1 in 500, 000 children in the UK.

Affected children develop Diabetes Mellitus (DM), typically in the first decade of life, Optic Atrophy towards the end of the first decade and Diabetes Insipidus (DI) and sensorineural deafness in the second decade. These clinical features form the acronym DIDMOAD, by which this condition is also known. Bladder dysfunction is typical and is seen in late first and second decades, with renal tract dilatation in the third decade.

Neurological deterioration predominates in the fourth decade. Respiratory failure secondary to brainstem atrophy leads to premature death[1]. In addition to DM and DI, gonadal atrophy is also described

The clinical features in different organ systems are attributed to abnormal production of wolframin, a protein important in protecting cells from endoplasmic reticulum stress[2].

Growth has been poorly characterised in case series published to date. Whilst insulin requirements are observed to be uncharacteristically low in at least the first few years of the disease, there is no published data on diabetes control in this group. There are concerns that poor diabetes control may impact on the progression of the disease due to increased metabolic stress.

In 2012 a nationally commissioned holistic multi-disciplinary specialist service for children and young people with WS was set up in Birmingham Children's Hospital to facilitate a better understanding of this complex multisystem disorder and provide expert advice to local health services providing medical care.

Aim

To determine growth and the prevalence of endocrine disorders in Wolfram Syndrome. We aimed to qualify therapies and the metabolic outcomes for DM in this group, and to determine the relationship of cranial MRI findings to clinical endocrine findings in children and young people (CYP) with WS.

Method

Examination of records of CYP attending Birmingham Children's Hospital for WS from 2012-2015, to determine height, weight, BMI, history, DM therapy, DI, thyroid and pubertal disorders. Results of gonadotrophin, sex steroid levels, TFTs, HbA1c, blood glucose, paired early morning plasma and urine osmolality. Height, weight and BMI were converted to standard deviation scores using UK 1990 growth data. Cranial MRI reports were examined for pituitary abnormalities.

Results

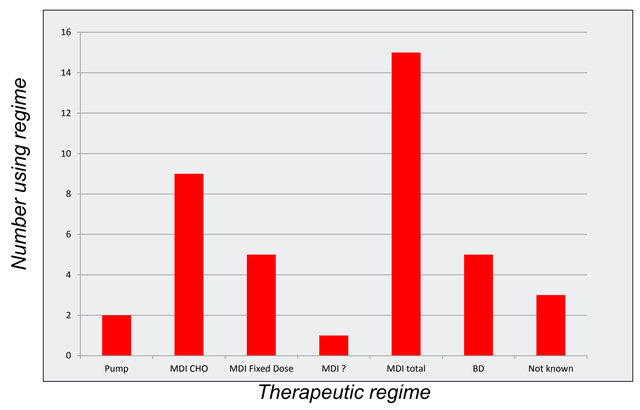
Twenty eight CYP have attended the clinic with an age range of 4.8 to 21.8 years. The median age is 13.8 years. There were 5 sibling pairs in attendance including 1 set of identical twins.

Growth The mean height, weight and BMI SDS(SD) were –0.226 (0.98), 0.195 (0.74) and 0.427(0.88) respectively. No significant sex differences were present.

Diabetes Mellitus Diabetes Mellitus was present in 89% of patients. Median HbA1c was 8.0%, with 35.6% achieving target HbA1c <7.5%. This compares with a median HbA1c in the National Audit 2013-14 of 8.5% in England and only 17.1% achieving HbA1c of <7.5%.

Figure 1 shows the diabetes therapy used in the clinic. Only 44% of CYP in the clinic were managed on intensive insulin therapy.

Figure 1. Diabetes therapy in Wolfram Syndrome.



Thyroid disease No CYP in the group had thyroid disease.

Diabetes Insipidus and cranial MRI
Cranial MRI was successful in 68% of the cohort. DI was present in 39%. In those patients with successful imaging posterior pituitary abnormality (absence or reduced T1 high signal of the posterior pituitary) was present in 100% with DI, and in 64% without DI. Of note two patients also had anterior pituitary abnormality (small anterior pituitary) without clinical evidence of either anterior or posterior pituitary failure.

Gonadal function Two CYP had hypergonadotrophic hypogonadism, requiring sex steroid replacement therapy.

Conclusion

This data implies children and young people with WS demonstrate normal growth and thyroid function.

Although outcomes are better than the national average for all forms of DM, the majority of CYP are treated more frequently with non-intensive insulin regimes, and have suboptimal diabetes control. This should be a focus for improving future outcomes, as poor metabolic control may increase cellular stress. Further studies are required to study evolution of pituitary abnormalities in WS.

Acknowledgements The children and young people under the care of Birmingham Children's hospital an living with Wolfram Syndrome

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