Addison’s disease and hypogonadism in a patient with cystic fibrosis

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A 42 year old man with known cystic fibrosis and secondary diabetes was diagnosed with Addison’s disease at the age of 19yrs. At the age of 35yrs he underwent lung transplantation for end stage pulmonary disease as a consequence of his CF. To manage these conditions he was maintained on insulin, corticosteroid and immunosuppressive therapy. At age 38yrs he presented with symptoms of low libido and was found to have hypogonadotrophic hypogonadism and was commenced on testosterone supplements. He was lost to follow up for a few years, however on representation it transpired that he had a family history including a brother who was also diagnosed with Addison’s disease at a similar age. Given the rarity of the diagnosis, the association with hypogonadotropic hypogonadism, and the apparent family history he was tested for a mutation in the DAX-1 gene.

His initial sex hormone profile revealed a testosterone of 3.3nmol/L, FSH 10.2 iu/L, LH 1.6 IU/L suggestive of hypogonadotrophic hypogonadism. His additional pituitary axes were within normal limits. An MRI head was unremarkable. DNA analysis revealed a heterozygous c.775T>C (p.Ser259Pro) substitution in exon 1 of the DAX gene which changes codon 259 from serine to proline.

DAX-1 is a nuclear receptor protein encoded by the NROB1 gene located on the X chromosome. It plays an important role in development of hormonal tissue. Mutations in this gene result in both X-linked congenital adrenal hyperplasia and hypogonadotrophic hypogonadism that classically present during childhood. Several mutations exist which result in a spectrum clinical presentations. Two previous cases have been described in the literature where there has been a delayed onset in presentation of both the adrenal insufficiency and hypogonadotropic hypogonadism. Finally the confirmation of the diagnosis by DNA analysis in this patient suggests the possibility of his brother having a similar mutation.