

Neuroanatomical associates of the cognitive and motor abnormalities found in children with Isolated Growth Hormone Deficiency

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Introduction: While growth hormone (GH) plays an important role in normal brain development, its effect on brain growth and cognition in GH deficient individuals continues to be debated. We have now investigated a cohort of children with isolated growth hormone deficiency (IGHD) using cognitive and motor skills assessment, volumetric MRI and diffusion tensor imaging (DTI) and compared the findings with those in a cohort of children with idiopathic short stature (ISS).

Methods: All children underwent a psychological assessment including the Weschler Intelligence Scale for Children (Fourth edition) and the Movement ABC (M-ABC) test. DTI was performed on a Siemens Avanto 1.5 Tesla MRI scanner. Following the acquisition of a T1-weighted volume scan 20 diffusion-sensitised directions were acquired with a b value of 1000 s mm^{-2} , this protocol was repeated 3 times. Correction for eddy current induced distortions, brain extraction, and calculation of diffusion tensor fractional anisotropy (FA) and mean diffusivity (MD) values was carried out using FSL tools (<http://www.fmrib.ox.ac.uk/fsl>). Analysis of the cognitive data showed that children with IGHD had significantly lower VIQ and M-ABC scores than controls. Corticospinal tract FA has previously been shown to correlate with motor impairment in individuals with chronic stroke and brain injury, and the basal ganglia have also been shown to play an important role in motor skills performance. We therefore performed corticospinal tract tractography using a probabilistic neighbourhood tractography (NT) approach (1) and acquired volumes for the basal ganglia from the 3-D datasets using the technique of Fischl *et al* (2). Brain volumes were compared using ANCOVA, controlling for age at scan, total brain volume (TBV) and sex. Partial correlation was used to assess the relationship between neural volumes and FA of the corticospinal tract to FSIQ, PIQ, VIQ and scores on the M-ABC (controlled for age at scan, sex and TBV).

Results: Fifteen children (mean 8.6yrs) with IGHD, and 12 (mean 8.5yrs) with ISS were studied. When compared to controls, children with IGHD had lower VIQ ($p < 0.02$) and M-ABC ($p < 0.02$) scores. VIQ scores correlated significantly with IGF1 and IGF1BP-3 standard deviation scores ($p < 0.03$, $p < 0.02$) in children with IGHD. Left thalamic ($p < 0.01$) and accumbens nuclei ($p < 0.01$), and left and right globus pallidum (L $p < 0.01$, R $p < 0.007$) were significantly smaller and left corticospinal tract MD significantly higher ($p < 0.03$) in IGHD (Figure 1). IGF-1 and IGF1BP-3 did not correlate significantly with FA or MD. Left corticospinal tract FA in the entire cohort correlated significantly with scores on performance IQ ($p < 0.007$), and the aim ($p < 0.006$), manual dexterity ($p < 0.02$) and total ($p < 0.007$) scores of the Movement-ABC test (Figure 2). In IGHD left corticospinal tract FA correlated significantly with M-ABC ($p < 0.04$) and performance IQ ($p < 0.04$) scores.

Conclusions: Our data suggest an effect of IGF1 and IGF1BP-3 on VIQ in IGHD. We also report, for the first time to our knowledge, the presence of white matter abnormalities in the corticospinal tract and basal ganglia abnormalities, in association with deficits in cognitive function and motor performance, in children with IGHD. These findings provide evidence that the GH-IGF-1 axis plays a significant role in neural development. The neural correlates of cognitive deficits we have identified in patients with IGHD may also offer insights into the pathogenesis of the cognitive decline associated with ageing and the somatopause. Follow-up studies are now required to determine whether GH treatment can rectify some of these abnormalities in brain and cognitive functioning as this would have major implications for clinical practice.

Figure 1 The difference in left corticospinal tract MD between children with IGHD and ISS

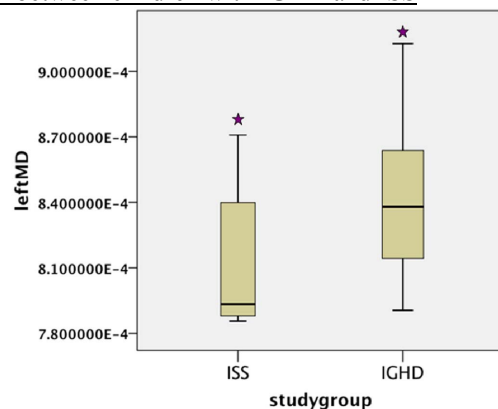
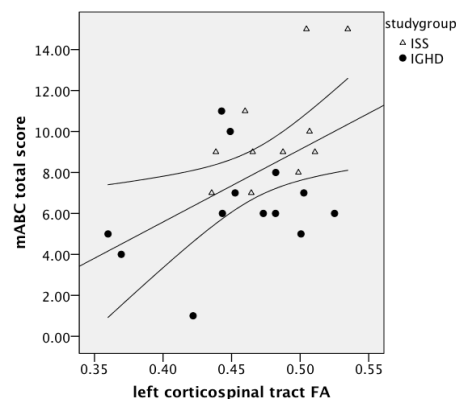


Figure 2 The relationship between total score on the Movement-ABC test and left corticospinal tract FA



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