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Original article

Assessment of metabolic changes within normal appearing gray and white matter in children with growth hormone deficiency: Magnetic resonance spectroscopy and hormonal correlation

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Abstract

Objective: The pathogenesis of idiopathic growth hormone deficiency (GHD) in children, including possible cerebral metabolic alterations, remains unclear. The aim of the study was to evaluate metabolic changes within the normal appearing brain in children with GHD using MR spectroscopy (MRS) and to correlate MRS measurements with hormonal concentrations and with pituitary gland size. *Methods:* Seventy children with GHD (mean age 7.8 yrs) and 11 healthy controls (mean age 8.4 yrs) were enrolled in the study. The MRS examinations were performed on a 1.5T scanner. Voxels were located in the posterior cingulate gyrus (PCG) and the left parietal white matter (PWM). The NAA/Cr, Cho/Cr and mI/Cr ratios were analyzed. The metabolite ratios, pituitary gland size and hormonal concentrations: growth hormone (GH) in two stimulation tests and GH during the night, as well as IGF-1 (insulin-like growth factor) and IGFBP3 (insulin-like growth factor-binding protein) levels were also correlated. *Results:* There was a significant ($p < 0.05$) decrease of the NAA/Cr ratios in PCG and PWM in children with GHD compared to the normal subjects. Other metabolite ratios showed no significant differences. We also found significant positive correlations between NAA/Cr ratio in PWM and IGFBP3 level, as well as with GH concentration in a stimulation test with glucagon. *Conclusions:* The reduction of NAA/Cr ratios may suggest loss of neuronal activity within normal appearing gray and white matters in children with GHD. MRS could be a sensitive marker of cerebral metabolic disturbances associated with GHD and maybe used as an additional indicator for therapy with recombinant GH.

Keywords: Growth hormone deficiency; Brain metabolism; Magnetic resonance spectroscopy; Insulin-like growth factor 1; Cognitive function

1. Introduction

Growth hormone (GH) is synthesized in the anterior part of the pituitary gland and, to a markedly lesser degree, by other tissues in the brain [1,2]. The production of GH is modulated by two hypothalamic hormones, growth hormone-releasing hormone

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(GHRH), which stimulates both the synthesis and secretion of GH and somatostatin which inhibits GH release in response to GHRH. GH also feeds back to inhibit GHRH secretion [3]. After excreting from the pituitary gland GH reaches the liver and due to this hormone action, the liver produces insulin-like growth factor-1 (IGF-1), which is the main anabolic mediator of GH activity. IGF-1 enters the blood stream where about 99% of IGF-1 is bound to the specific binding proteins and acid labile subunit (ALS) that significantly prolong the half-life of the peptide. The most important binding protein is the insulin-like growth factor-binding protein 3 (IGF-BP3), which bands up to 90% of IGF-1. Then the complex IGF-1/IGF-BP3 reaches the bones and muscles, which are the main final target organs for IGF-1 action [3,4].

For a long time, GH and IGF-1 have been recognized mainly for their critical role in achieving normal height. Recently, it has been proved that the GH/IGF-1 axis is involved not only in brain growth, development and myelination, but also in brain plasticity as rendered by neurogenesis. This may be associated with various cognitive effects of GH/IGF-1 [2,5–11]. However, little is known about the influence of growth hormone deficiency (GHD) on brain structure and possible metabolic alterations, especially in children [1,5,12].

Magnetic resonance spectroscopy (MRS) has enabled the in vivo evaluation of certain metabolites in a variety of pathologic processes affecting the central nervous system (CNS). MRS is capable of detecting the changes in metabolite profiles in normal appearing white matter (NAWM) and normal appearing gray matter (NAGM) [13–15]. Therefore, this advanced MR technique may offer a potentially unique insight into the pathophysiology of CNS changes associated with GHD. Moreover, it should be stressed that in the available world literature there are no articles concerning the analysis of metabolic alterations within NAWM and NAGM in children with GHD.

The aim of the study was to evaluate the metabolic changes within the normal appearing brain in children with GHD using MRS, as well as to correlate MRS measurements with hormonal concentrations and the size of the pituitary gland. To the best of our knowledge this is the first study focusing on the role of MRS in assessment of metabolic disturbances associated with GHD in children.

2. Materials and methods

2.1. Patients

Seventy children with idiopathic growth hormone deficiency (24 girls and 46 boys; mean age 7.8 yrs, ranging from 3 to 15 yrs), as well as 11 healthy children (7 girls and 4 boys, mean age 8.4 yrs, ranging from 3 to 14 yrs) were prospectively enrolled in the study. The diagnosis of GHD in childhood was based on the combination of auxological and hormonal criteria – decreased GH peak (below 10 ng/ml) in 2 stimulating tests – with oral clonidine 0.15 mg/m^2 and i.m. glucagon 30 μg/kg i.m. (not exceeding 1 mg). The main inclusion criteria were as follows: short stature (height below 2 standard deviations (SDs) from the population mean), slow height velocity (below 10th centile) and GHD (peak GH concentration below 10 ng/ml in two stimulation tests), as well as delayed bone age as assessed by the Greulich-Pyle method [16]. The main radiological criteria were a normal appearing brain and lack of focal lesions within the pituitary gland. The MR examinations in children with GHD were performed prior to the commencement of growth hormone treatment.

The study was conducted in accordance with the guidelines of the local University Ethics Committee for conducting research involving humans. Parents or legal guardians of all patients provided their signed informed consent to participate in the examination.

2.2. Endocrinological assessment

The endocrinological evaluation consisted of hormonal concentration measurements as follows: the IGF-1, IGF-BP3 levels, as well as the GH concentrations during the night, GH concentration in two stimulations tests: with glucagon and clonidine. The latter included the GH concentration measurement after i.m. administrations of glucagon in the dosage of 30 μg/kg and oral administration of clonidine in the dosage of 0.15 mg/m^2. Blood samples for GH were collected at time 0 and after 90, 120, 150 and 180 min after i.m. administration of glucagon, as well as at time 0 and after 30, 60, 90 and 120 min after oral administration of clonidine. During the night test, GH concentrations were measured at time 0 and after 60, 90, 120, 150 and 180 min after falling asleep.

Growth hormone concentrations were measured using hHG IMMULITE and DPC assay, calibrated to WHO IRP/80/505 standard. Serum IGF-1 and IGFBP-3 concentrations were assessed by IMMULITE DPC assay, calibrated to WHO NOBSC 1st IRR/87/518 standard for IGF-1 and WHO NIBSC Reagent 93/560 standard for IGFBP-3.

2.3. The control group

As MR examination in the youngest children requires sedation, ethical reasons precluded us from recruiting healthy volunteers to make up the control group. Therefore we enrolled in the study only children who were referred for MR examination of the brain due to a variety of clinical reasons which are shown in Table 1. The control subjects fulfilled the following clinical criteria: