Cognition in the adult with childhood-onset GH deficiency

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Abstract

The GH/IGF1 axis may play an important role in cognitive function. This theory is supported by the finding that both GH and IGF1 receptors are located in several brain areas such as the hippocampus, a brain area that is known to play an essential role in cognitive processes, especially memory and learning. However, the exact mechanism by which the GH/IGF1 axis influences the cognitive functions is still unknown. Furthermore, little is known about the cognition in adults with both childhood-onset and adult-onset GH deficiency (CO-GHD and AO-GHD). Recent data indicate that cognitive function, particularly attention and memory, in adults with GHD might be impaired. To date, only a limited number of studies have been conducted to study the effects of GH replacement therapy on cognitive function in adults with GHD. In this paper, the results of studies on cognitive functioning in GHD patients, in particular the results of the studies performed in adults with CO-GHD, and the effects of GH replacement therapy in these patients, will be discussed.

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Introduction

In adults with growth hormone deficiency (GHD), both physical and psychological performances are reported to be impaired when compared with healthy, age-matched controls. For example, body composition changes, namely an increased fat mass and decreased lean body mass, a reduced bone mass and impairments in quality of life have been observed. GH replacement therapy seems to have beneficial effects in these patients (1). In elderly patients, a positive correlation between serum insulin-like growth factor-1 (IGF1) levels and cognitive function has been reported in a number of cross-sectional epidemiologic studies (2–5). However, little is known about the cognitive function in adult GHD patients. In the past years, only a small number of studies on cognitive performance in adults with GHD have been performed and the results indicate that cognitive function might be impaired. The underlying mechanism is not fully understood, but there are indications that the GH/IGF1 axis may play a direct role. For example, *IGF1* gene expression was observed in the hypothalamus, hippocampus, olfactory bulb, cerebellum, neocortex and striatum of young adult brains (6). Furthermore, IGF1 receptors have been localized in the brain, with the highest densities in the hippocampus, amygdala and parahippocampal areas (7). GH receptors

(GHRs) have been localized in the brain areas such as the choroid plexus, thalamus, hypothalamus, pituitary, putamen and hippocampus (8, 9). Since high levels of GHRs and IGF1 receptors are found in brain regions that are known to be of importance in cognitive functioning, e.g. the hippocampus, amygdala and parahippocampal areas, GHD may affect cognitive function and GH replacement therapy may counteract these alterations in cognitive performance (10).

There are also indications that GH may pass the blood–brain barrier (8, 11). Few studies have been performed in which GH and IGF1 concentrations in the cerebrospinal fluid (CSF) have been analysed. Johansson *et al.* investigated GH and IGF1 levels in CSF before and after treatment with s.c. recombinant human GH (rhGH) (11). They observed a significant increase in IGF1 and a tenfold rise in GH concentration in CSF after GH substitution. In another study, the rise in GH concentration in the CSF was 3.7-fold after treatment with GH, and the GH concentration in CSF was found to be related to the administered GH dose (12). Furthermore, rhGH treatment seems to alter CSF neurotransmitter levels (11–15). After GH substitution therapy, CSF concentrations of vasointestinal peptide, noradrenaline and homovanillic acid, a dopamine metabolite, decreased and the concentration of aspartate increased (11–13, 16). Aspartate is an excitatory amino acid and is a ligand for the *N*-methyl-*D*-aspartate (NMDA) receptor. The NMDA receptor is thought to be involved in memory processes in the hippocampus of the mammalian brain. Therefore, the reported increase in

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aspartate levels in the CSF may play an important role in cognitive performance (12). Data on the concentration of β -endorphin in CSF after GH substitution therapy are contradictory (11, 12).

Altogether, there is convincing evidence for a role of the GH/IGF1 axis in cognitive functioning. In children with GHD, a deterioration in cognitive function has been observed (17, 18). Since some adults with GHD complain of impaired memory and attention, adults with GHD might also suffer from decreased cognitive functioning. In the past years, a limited number of studies have been performed in GHD adults to gain more insight into the consequences of GHD on cognition and the effects of GH replacement therapy on cognitive performance in adults with GHD. Both cross-sectional and prospective studies have been carried out. Some of these studies focused on adults with childhood-onset (CO) GHD, others on adult-onset (AO) GHD or both. In this paper, the results of the studies on cognitive functioning in GHD patients, in particular the results of the studies performed in adults with CO-GHD, and the effects of GH replacement therapy in these patients, will be discussed.

Cognition in adults with CO-GHD and the effects of GH replacement therapy

A deterioration in cognitive function has been observed in children with GHD (17, 18). Deijen *et al.* investigated iconic memory (IM), short-term memory (STM), long-term memory (LTM) and perceptual-motor skill in 48 adult men with CO-GHD and 41 healthy controls (19). On the IM test, on one of the STM tests and on all the LTM tests, GHD patients performed worse in comparison with normal controls. Furthermore, IQ score was lower in GHD patients than in controls. Of the 48 CO-GHD men, 31 had multiple pituitary hormone deficiency (MPHD) and 17 suffered from isolated GHD (IGHD). In MPHD patients, perceptual-motor skill and memory performance were impaired when compared with healthy controls. However, only a subnormal memory performance was observed in IGHD patients, indicating that MPHD and IGHD are different disease entities. Also, a positive association between serum IGF1 level and both education level and IQ score was observed (19). In a study performed by Lijffijt *et al.*, attention and cortical activities were evaluated by measuring event-related potentials (ERPs) during a selective attention task in ten CO-GHD patients and compared with matched controls. Patients showed an impairment in selective attention and a decrease in an attention-related brain potential, which appears to be associated with functioning of the anterior cingulate cortex (20).

Cognitive performance and parameters for neural integrity were evaluated by Van Dam *et al.* using magnetic resonance spectroscopy to assess brain *N*-acetylaspartate (NAA)/choline ratios in 11 CO-GHD adults in comparison with 9 normal controls (21). An

increased level of choline reflects increased membrane synthesis or breakdown, and NAA is thought to be a marker for neural density and integrity. Tests for memory, mental processing speed, reading ability and executive function were used to assess neuropsychological performance. In patients, impairments were found in verbal memory recall, measured by the 15-word delayed recall score, and on the trail making A test, which measures planning of behaviour, processing speed and attention. Furthermore, in GHD patients both decreased NAA levels and NAA/choline ratios were found, and choline levels were increased, which may reflect an altered neural integrity (21). In another study, in which functional magnetic resonance imaging (fMRI) was used, Arwert *et al.* report a subnormal memory speed, but a normal quality of memory performance in 13 CO-GHD adults in comparison with normal controls. In patients, activity in several brain areas, e.g. dorsolateral/ventrolateral prefrontal cortex, anterior cingulate cortex, parietal cortex, supplementary motor and motor cortex, thalamus and precuneus area, was increased. The authors suggest that the decrease in memory speed found in this study may be a result of the compensatory use of different brain regions (e.g. dorsal prefrontal brain regions) (22).

One of the first studies on the effects of GH replacement therapy on cognitive function in adults with CO-GHD was performed by Almqvist *et al.* (23). Five CO-GHD patients received native human GH and biosynthetic methionyl human GH for two separate 4-week periods and cognitive performance was measured by five psychometric tests before and after each treatment period. An improvement in performance on the face recognition test was observed. In another study, intellectual tasks were evaluated in eight adults with CO-GHD before and after 6 months of rhGH therapy (24). The results of this study show an overall improvement of intellectual tasks after 6 months of rhGH replacement therapy. In a double-blind, placebo-controlled, cross-over study, the effects of 12 weeks of recombinant methionyl GH treatment on cognitive functioning in six patients with AO-GHD was evaluated by performing a reaction time test and a Symbol-Digit Substitution Test. Although the patients reported improvements in vitality and alertness, GH treatment did not result in significant changes in cognitive performance. As the authors suggest, this might be a result of large interindividual variations and already high baseline scores (25). Lasaite and colleagues investigated the effects of 6 months of GH replacement therapy on cognitive performance, measured with the Digit Symbol Test and the Digit Span Subtest of the Wechsler Adult Intelligence Scale (26). Cognitive performance was found to improve after GH substitution, in particular higher scores on tests measuring incidental learning and psychomotor speed were observed.

A fMRI study performed by Arwert *et al.* showed that 6 months of GH substitution therapy in 13 CO-GHD adults improved both long-term and working memories

(27). Furthermore, they demonstrated an increase in efficiency of working memory-associated cortical regions in the GH-treated patients when compared with the placebo group. Deijen and colleagues performed a study in which they evaluated the effects of 2 years of GH substitution on cognitive performance in 48 CO-GHD men (13). The first 6 months of the study had a placebo-controlled design and thereafter patients were followed for another 18 months in an open-label phase. Patients were randomly assigned to placebo or one of the GH treatment groups (GH dose 1, 2 or 3 IU/m² respectively) and STM, LTM, IM and perceptual-motor skill were assessed. After 6 months of treatment, both STM and LTM improved in the group receiving supraphysiological GH therapy only. However, after 1 year of GH treatment, memory performance normalized in patients with IGF1 levels within normal reference values, and this effect was maintained during the second year of GH substitution therapy. There were no changes in perceptual motor skill. A 10-year follow-up study of the same patient group showed that the improvement in memory function was still present after 10 years of GH treatment when compared with baseline values (28).

Cognition in adults with AO-GHD

Baum *et al.* performed a 18-month randomized, double-blind, placebo-controlled study in 40 men with AO-GHD and found baseline scores of verbal learning and delayed visual memory to be low, although within the normal range (29). After 18 months of GH replacement therapy, no significant improvements in cognitive performance were found in the GH-treated patients when compared with the placebo group (29). By contrast, Bülow *et al.* investigated cognitive function in 33 women with AO hypopituitarism and compared the results with 33 age, gender and residence matched controls. Cognitive performance was studied by seven neuropsychological tests, namely vocabulary (SRB:1 vocabulary test, a Swedish vocabulary test), perceptual speed (WAIS-R Digit Symbol), spatial ability (WAIS-R Block Design), spatial learning (Austin Maze test), verbal memory (Cronholm-Molander verbal memory test) and reaction time (Automated Psychological Test (APT) Two-way Reaction Time and APT Inhibition). The patients scored significantly lower on four of the seven tests, namely tests of vocabulary, perceptual speed, spatial and learning speed and one of the tests measuring reaction time (30). As the authors suggest, several other factors, such as transfrontal surgery, radiotherapy, visual impairments or suboptimal hormonal substitution, might have negatively affected the disturbances in cognitive function found in this study. Oertel *et al.* performed an 18-month placebo-controlled study in 18 AO-GHD patients and found that attention, measured using a digit cancellation test and a Trail Making Test, improved after at least 3 months of GH

replacement therapy. Verbal memory (verbal STM and LTM, measured using a text reproduction task) and non-verbal intelligence (measured with the Raven Standard Progressive Matrices test) did not improve after 18 months of GH substitution (15). Sathivageeswaran and colleagues studied elderly patients with AO-GHD in a double-blind, placebo-controlled study. Discrete beneficial effects of GH treatment after 24 weeks of GH therapy on cognition (e.g. the digit learning test) were found. This difference between the GH and the placebo group occurred because of both an increase in cognitive function in the GH-treated group and a decrease in the placebo group. After 52 weeks of treatment, however, there were no significant differences in psychological performance between the GH-treated group and the placebo group (31).

In women with GHD as a result of Sheehan's syndrome, cognitive functions were assessed by measuring P300 event-related potentials (ERPs) (14). At baseline, mean ERP latencies (as a marker of the speed of stimulus evaluation) were significantly prolonged when compared with those of normal controls. A significant decrease in P300 latencies to normal values was observed in patients after 6 months of physiological GH replacement therapy, indicating a significant increase in cognitive performance following 6 months of GH treatment. Soares *et al.* studied cognitive function in nine GHD adults, two with CO-GHD and seven with AO-GHD, before and after 6 months of rhGH treatment in a double-blind placebo-controlled trial (32). Neuropsychological performance was evaluated using measurements of attention (Digit Span Forward, Digit Span Backward, Verbal Fluency, trail making A test and Stroop Colour Test) and cognitive tests (Vocabulary, Block Design, Comprehension, Picture Arrangement, Similarities and WAIS-R). After 6 months of GH replacement therapy, significant improvements were reported in Digit Span Backward, Verbal Fluency, Vocabulary, Comprehension and Picture Arrangement.

Discussion

In the past years, a limited number of studies on cognitive performance in both CO- and AO-GHD adults have been performed. These studies indicate that cognitive function might be impaired, although the results are not conclusive and difficult to interpret, since heterogeneous types of neuropsychological tests have been used and most studies were performed in small patient groups. Recently, two meta-analyses have been performed on patient-related outcomes and cognitive function. The first meta-analysis was performed by Arwert *et al.* and comprises all clinical trials from 1985 to 2004, concerning patient-related outcomes and cognition in both CO- and AO-GHD patients before and after GH replacement therapy (33). However, cognitive performance was evaluated in only four of these studies. After 6 months of GH treatment, no

significant improvement in cognitive function was found in GHD patients. Comparison of the GH-treated patients with the placebo group was not possible since only two of the four studies had a placebo-controlled design (33). The second meta-analysis comprised 13 studies, 5 cross-sectional studies on cognitive impairments in GHD patients and 8 prospective studies in which the effects of GH replacement therapy on cognitive function was evaluated. In GHD patients, moderate to large impairments in attention, memory and executive function were found when compared with matched controls. Furthermore, this meta-analysis shows that GH substitution might have beneficial effects on these impairments, since cognitive function continuously increases with longer treatment duration (34). This meta-analysis also concerned studies in both CO- and AO-GHD patients, so it is not possible to draw any conclusions about a possible difference between these two groups.

Altogether, memory, attention and executive functions seem to be impaired in adults with CO-GHD, although the impairments may be subtle and depend on the tests being used. Since impairments in cognitive function are reported in both MPHD and IGHD patients, it is likely that this impaired cognitive performance is a specific consequence of GHD (19). Available data so far indicate that in patients with CO-GHD other aspects of cognitive function are disturbed when compared with patients who become GHD during adult life as described above (35). In a number of studies, cognitive function, in particular memory performance and attention, seems to improve with GH replacement therapy and this improvement is greater than that expected by practice (34). However, the data on cognitive performance in both adults with CO- and AO-GHD deficiencies and the effects of GH replacement therapy are limited, and further research in this area is needed. For example, high-resolution fMRI scans could be performed. Ideally, these scans should be done in large cohorts of both CO-GHD and AO-GHD patients, preferably with IGHD, before and after treatment with GH in a placebo-controlled randomized design.

Disclosure

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