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GH Deficiency as The Most Common Pituitary Defect After TBI: Clinical Implications

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Abstract. **Recent studies have demonstrated that hypopituitarism, and in particular growth hormone deficiency (GHD), is common among survivors of traumatic brain injury (TBI) tested several months or years following head trauma. In addition, it has been shown that post-traumatic neuroendocrine abnormalities occur early and with high frequency. These findings may have significant implications for the recovery and rehabilitation of patients with TBI. The subjects at risk are those who have suffered moderate-to severe head trauma although mild intensity trauma may precede hypopituitarism also. Particular attention should be paid to this problem in children and adolescents. GH deficiency is very common in TBI, particularly isolated GHD. For the assessment of the GH-IGF axis in TBI patients, plasma IGF-I concentrations plus GH response to a provocative test is mandatory. Growth retardation secondary to GHD is a predominant feature of GHD after TBI in children. Clinical features of adult GHD are variable and in most obesity is present. Neuropsychological examinations of patients with TBI show that a significant portion of variables like attention, concentration, learning, memory, conceptual thinking, problem solving and language are impaired in patients with TBI. In the few case reports described, hormone replacement therapy in hormone deficient head-injured patients resulted in major neurobehavioral improvements. Improvements in mental-well being and cognitive function with GH replacement therapy in GHD adults have been reported. The effect of GH replacement in posttraumatic GHD needs to be examined in randomized controlled studies.**

Key Words. **growth hormone deficiency, traumatic brain injury**

The frequency of growth hormone deficiency (GHD) is reported to be one in 3000 to one in 4000 [1]. The incidence of isolated GHD hormone relative to multiple pituitary deficiencies varies greatly. In some large post-marketing surveillance databases isolated GHD occurs appoximately in 10% [2] while in a French study up to 20% [3]. Some apparent differences are probably due to great variation in tests and criteria used.

Acquired GH Deficiency in Adults Secondary to Structural Lesions or Trauma

Patients with large non-functioning pituitary adenomas, patients following transsphenoidal surgery for pituitary adenomas and patients who have had irradiation of pituitary tumors or other head/neck brain tumors are at risk of GHD. Studies in these patients show that GH is generally the first lost [4]. Many studies have shown that the greater the number of deficits occuring of other pituitary hormones the likelihood of GHD increases [5,6].

Adult GHD in Patients with Childhood Onset of GHD

Several genetic abnormalities have been identified in children who were thought to have idiopathic growth hormone deficiency. GHD in childhood is associated with structural defects of the brain and with midline facial defects. But GHD in adults with childhood onset can be acquired due to trauma either perinatal or postnatal, infections, CNS tumors, post cranial irradiation and chemotherapy [1].

GH Treshold Definitions of Adult GHD

In real life there is a spectrum of GH deficiency from severe, partial to not at all. The diagnosis of GH deficiency is based on an inadequate response of the hormone to provocation. The situation is complicated by the availability of many provocation tests and many assays for its measurement [7]. The consensus has recommended that at least two tests of GH provocation are needed to establish a diagnosis of GH deficiency or insufficiency [4]. In those with defined pathology in the hypothalamic-pituitary region (a history of surgery, irradiation, genetic defect), one test will suffice. Even with these criteria,most patients can have a reverse in terms of biochemical GH deficiency when retested. The stimulated GH levels currently used are somewhat arbitrary and are based on relative cutoffs between normal population and patients.

Among the provocative tests the insulin tolerance test is the diagnostic test of choice and the criterion for diagnosing GHD severe enough to warrant therapy is a peak GH of less than 3 mcg/L [8]. Alternative tests have been proposed as GHRH+arginine defining severe GHD with a cut off point for GH < 9 μg/L [9,

10], GHRH+GHRP-6 defining severe GHD with a cut off point for GH < 10 μg/L [11] and glucagon defining severe GHD with cut off point for GH< 3 μg/L. Those individuals with clearly low GH values on stimulation could be considered GH deficient and possibly offered GH therapy.

How Useful is IGF-1 Measurement?

Most studies show that about one third patients with GHD diagnosed by stimulated GH levels have IGF-I levels in the normal range [12]. Not a lot of GH is needed to get normal IGF-I levels. Thus what GH level is truly normal or abnormal with respect to IGF-I or other aspects of GH action is not clear. IGF-1 < 2 SDS high likelihood of severe GHD. IGF1 > 2SDS low likelihood so IGF1 plus l provocative test is needed. Low plasma IGF-I and IGFBP3, both of which are regulated by GH, might aid in diagnosis, although in isolation, the specificity and sensitivity of the test are poor.

Growth Hormone Deficiency (GHD) in Traumatic Brain Injury (TBI)

The most common isolated deficit is GHD and this fits well with studies showing that GHD is usually the first pituitary deficit to appear Fig. 1. GHD is present in 10–25% of subjects as documented by dynamic testing in most of the recent studies [13–18]. These findings do not correlate to the severity of TBI according to GCS scores. A prospective study conducted in Italy on the incidence of hypopituitarism following TBI showed that at three-month testings impaired GH response to GHRH+arginine in 25% [16] Fig. 2. When patients were retesed at 12 months post trauma then some isolated pituitary insufficiencies recorded at short term were no longer present implying that pituitary function in brain injured patients may improve over time and transient hypopituitarism would relect effective repair of the hypothalamus-pituitary injury but GH-deficiency was transient only in 2% of the TBI patients. Thus the incidence of severe GH deficiency at 12 months remains very remarkable, approximately 20% [19].

The prevalence of GHD in other series is slightly lower. 10% of patients with TBI were severely GHD when tested with GHRH+GHRP-6 test [18] Fig. 3 or when tested with two different stimulation tests : glucagon and insulin induced hypolgycemia test [17]. The percentage of severely impaired GH response to such a powerful provocative stimulus as is the GHRH+GHRP-6 test, in our study is similar to the results obtained by Aimaretti et al. with GHRH+arginine test. We have previously shown that both tests are similar in their capability to diagnose GHD in adults. On its own total IGF-I levels were not a reliable predictor for diagnostic screening of adult GHD even though GH- deficient patients had lower serum concentrations than GH-sufficient patients. Multifactorial regression analysis showed GH deficiency to be associated with higher BMI but unrelated to age and gender [17].

Posttraumatic anterior pituitary failure has also been sporadically reported in children [20]. Among other anterior pituitary hormone defects, growth retardation secondary to GHD was a predominant feature. Only one patient had diabetes insipidus.The prevalence of traumatic origin among the hypopituitary dwarfs in that study was 3.7%.

The reason why GH is the most sensitive anterior pituitary hormone which becomes deficient in patients with TBI is unclear particularly since the physiopathological mechanisms of hypopituitarism induced by brain injury are not well defined and need further studies. The infundibular-hypothalamic-pituitary structure is very fragile due to its peculiar anatomical and vascular structure. The vascular hypothesis is supported by necrotic, ischemic, hypoxic changes at

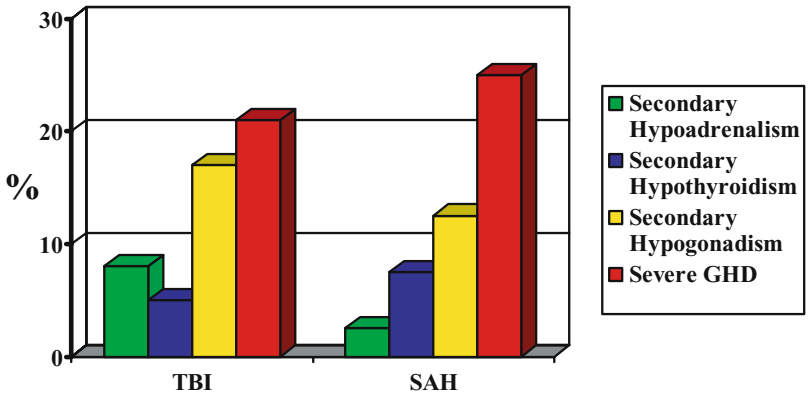

Fig. 1. *Percentage of single pituitary deficits in patients with traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), 3 months after the pathological event-Reproduced by the kind permission Blackwell from G.Aimaretti et al., Clin.Endocrinol. 61:320–326, 2004.*

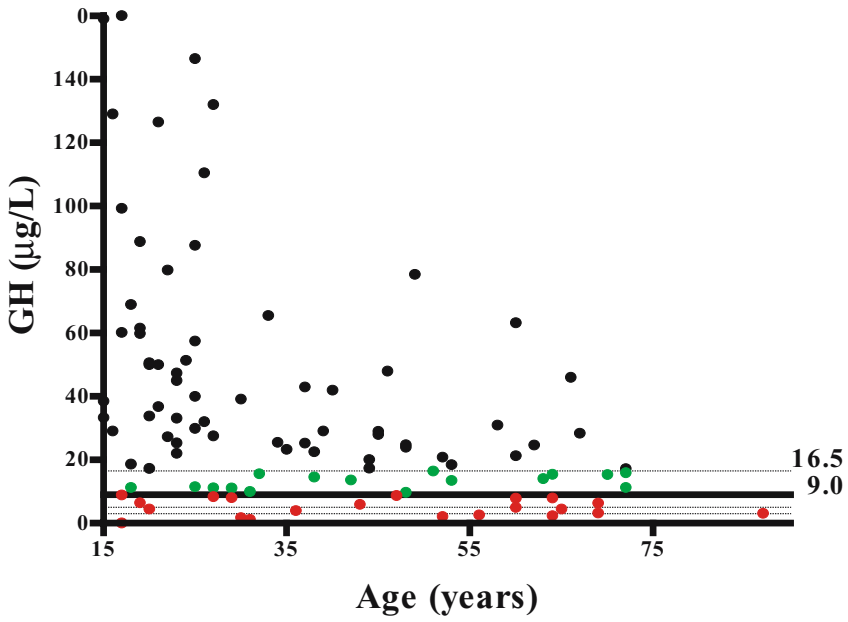

Fig. 2. *Individual peak GH responses to GHRH+ arginine (ARG) test in patients with traumatic brain injury (TBI) 3 months after the pathological event. The continous line represnets the 1st centile limit of normal response to GHRH+ARG test.The other lines represent a) the 3rd centile limit of normal response to GHRH+ARG test (= 16.5 µg/l);b) the 3 rd centile limit of normal response to ITT test i.e. the so called gold standard test (= 5,0 µg/l);c) the 1st centile limit of normal response to ITT test (= 3 µg/l); severe GHD is demonstarted by ITT test below this limit—Reproduced by the kind permission Blackwell from G.Aimaretti et al., Clin.Endocrinol. 61:320–326, 2004.*

the pituitary (vulnerability of the somatotrophs and gonadotrophs located in the lateral wings od the anterior pituitary) and at hypothalamic level (possible vulnerability of GHRH neurons) [13]. Generally, patients with brain injury have suffered ischemic insult which leads to oxidative stress and excitotoxicity and together with inflammation leads to accelerated neuronal cell death by means of either apoptosis or necrosis [21]. Shearing lesions at the hypothalamus are also possible. GH-releasing hormone (GHRH) neurons in the hypothalamus seem to be highly vulnerable to injury by their location.

What are Adult Strategies in GH Replacement?

Adult GHD is clearly a hormone deficiency syndrome [22,23]. The syndrome consists of the variable presence of increased body fat and decreased lean body mass, decreased bone mass and incresed fracture rate,impired cardiac function and reduced muscle strength.GHD in adults shares a number of characteristics of the metabolic syndrome including hypertension, abdominal obesity, insulin resistance, dyslipidemia and enhanced thrombotic factors.In addition, quality of life is impaired, with reduction in physical and mental energy, increased anxiety, dissatisfaction with body image and poor memory [24–26]. There is evidence of increased cardiovascular mortality in hypopituitary patients without GH therapy [27]. In a recent analysis of 289 hypoptuitary adults who received GH replacement, mean duration of treatment 5yr, overall mortality was similar to that in the normal population [28].

The question arises as to whether patients with isolated growth hormone deficiency (IGHD) might differ in clinical presentation or in responsiveness to GH replacement from those with multiple pituitary hormone deficiencies (MPHD) receiving conventional replacement therapy with corticosteroids, thyroxine and sex steroid hormones.A recent analysis of patients retreived from a large database demonstrated that the magnitude of change in a wide variety of endpoints was not significantly different between IGHD and MPHD patients after 1 year of GH replacement [2]. The favourable effects upon waist-hip ratio, waist circumference, lean and fat mass, lipid concentration, and the AGHDA score were clearly present and comparably favourable in both adult onset and childhood onset GHD groups. These findings can be considered strong arguments in favour of GHD acting as a distinct deleterious entity. The conclusion of that study was that GHD had clinical impact particularly on quality of life and thus isolated GHD must be recognized and treated accordingly.

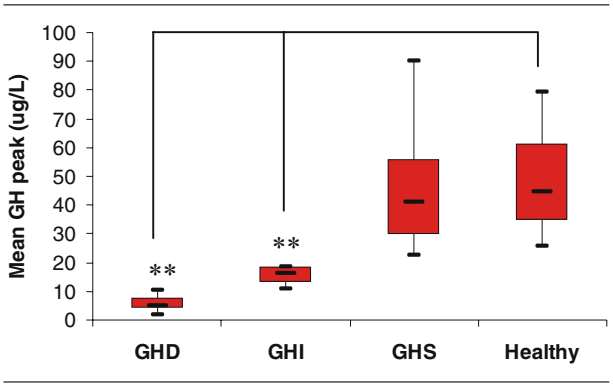

Fig. 3. *Box and whisker plots representing the peak GH responses to the combined GHRH+GHRP-6 test in traumatic brain injury (TBI) patients and healthy subjects.The lower boundary of the box marks the median and the upper boundary of the box indicates the 75th percentile.Error bars above and below the box indicate the 90th and 10th percentiles ** $p < 0.01$ GHD: GH deficiency GHI: GH insufficient GHS:GH sufficient—Reproduced by the kind permission of Editirice Kurtis in Popovic et al. J. Endocrinol. Invest. 27:1048–1054, 2004.*

Neurobehavioral Impact of Hypopituitarism

Neuropsychological examinations of patients with TBI show that a significant portion of variables like attention, concentration, learning, memory, conceptual thinking, problem solving and language are impaired in patients with TBI [29]. In the few case reports described, hormone replacement therapy in hormone deficient head-injured patients resulted in major neurobehavioral improvements [30]. Impaired well-being, attention and memory disabilities have been previously reported in patients with hypopituitarism on adequate adrenal, thyroid and sex hormone replacement therapy but without GH replacement [24–26]. Hypopituitary patients treated for pituitary disease had more symptoms of mental distress and performed less well in neuropsychological tests compared to matched population controls and this was possibly due to neurosurgery, radiotherapy and unphysiological hormone replacement.The hypopituitary women in one study had significantly lower scores in 4 out of 7 neuropsychological tests,including tests of vocabulary,perceptual speed, spatial learining as well as in one reaction time tests [26]. The importance of these neuropsychological examinations is in trying to define neurobehavioral domains potentially affected by GH and other hormonal deficiencies in order to monitor treatment effects.We have found that in TBI patients peak GH levels after GH provocative testing positively correlated with verbal learning and verbal short term memory. Psychiatric testing showed depression and phobic anxiety and psychotism to be prominent in TBI patients. Paranoid ideation and somatization negatively correlated with peak GH response to the provocative test [18].

Increasing consideration has been given to potential effects of GH on the central nervous system [31]. After subcutaneous injection GH reaches the cerebrospinal fluid (CSF) in humans [32]. GH receptors are mainly found in the choroid plexus, thalamus, hypothalamus, pituitary, putamen and hippocampus, whereas IGF-I receptors are concentrated in the hippocampus and parahippocampal areas [33]. An effect of GH replacement on human brain neurotransmitters has led to changes in the levels of neurotransmitters in the cerebospinal fluid,a finding that may be of particular significance for cognitive functions [32,34–37]. These studies showed a significant decline in the CSF concentration of the dopamine metabolite homovanillic acid (HVA) in patients on GH treatment.This effect on neurotransmitter turn-over is comparable to the reported reduction of HVA in the CSF of depressed patients after successful treatment.

The question of the influence of the somatotropic system on cognitive functions has been the subject of debate for a long time and still is.In view of the recent findings of positive effect of GH replacement on cognitive performance in adult patients with hypopituitarism the benefit of hormone replacement therapy on cognitive functioning and mental distress in post-traumatic hormone deficient patients, need additional research.

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