Amelioration of cognitive impairment following growth hormone replacement therapy: A case report and review of literature

Jung-Tung Liu, Pen-Hua Su

ORCID number: Jung-Tung Liu 0000-0003-1260-0022; Pen-Hua Su 0000-0001-6627-9364.

Author contributions: Liu JT was the neurosurgeon of the patient. Both the authors collected the patients’ clinical data, reviewed the literature, drafted and revised the manuscript, and approved the final version to be submitted.

Informed consent statement: Written informed consent was obtained from the patient before the publication of this report and accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Abstract

BACKGROUND
Stroke is one of the leading causes of death and disability worldwide. In patients suffering from strokes and other acute brain injuries, the prevalence of pituitary dysfunction is high, and growth hormone deficiency is commonly found. Previous studies have demonstrated that administration of recombinant human growth hormone provides adult growth hormone deficiency (AGHD) patients with beneficial effects such as improving body compositions and quality of life. Nevertheless, other physiological benefits of growth hormone substitution are still controversial and inconclusive.

CASE SUMMARY
A female with a history of hypertension suffered intracranial hemorrhage, intraventricular hemorrhage, and hydrocephalus at 56 years of age. Her mobility, fluency of speech, and mentality were impaired ever since the event occurred. After five years, the 61-year-old patient was further diagnosed with AGHD and received six-month growth hormone replacement therapy (GHRT). After six months of GHRT, the patient’s body composition was improved. A substantial improvement in Mini-Mental State Examination score was also observed, accompanying with ameliorations in mobility, fluency of speech, and mentality.

CONCLUSION
In addition to improvements in body composition, GHRT for AGHD may provide further beneficial effects in patients with cognitive or motor impairments due to intracerebral hemorrhage.
and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/License

**Key Words:** Cerebral hemorrhage; Growth hormone; Cognitive dysfunction; Case report

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** We present a case report of a female patient suffered nontraumatic intracerebral hemorrhage and was diagnosed with adult growth hormone deficiency five years later. Unexpected improvements in cognitive function, fluency of speech, and mobility were observed after six months of growth hormone replacement therapy, suggesting that growth hormone replacement therapy may provide further beneficial effects in adult growth hormone deficiency patients with cognitive or motor impairments due to intracerebral hemorrhage.

**INTRODUCTION**

Stroke remained one of the leading causes of death throughout the world and was among the top ten diseases contributing to years lived with disability in 2010[1]. The long-term disability caused by stroke results in immense health and economic burdens. As a subtype of stroke, nontraumatic intracerebral hemorrhage (ICH) accounts for around 10% of all strokes, with hypertension being the most significant risk factor[2]. The long-term neurologic sequelae of stroke can result in significant impacts on the patients’ cognitive function, motor performance, and quality of life.

Growth hormone (GH) plays a crucial role in regulating physiological and metabolic status in adults. Development of neuropsychiatric-cognitive, cardiovascular, neuromuscular, metabolic, and skeletal problems can be observed in adult patients with growth hormone deficiency[3]. While it is known that pituitary tumors, craniopharyngioma, and idiopathic GHD are major causes of adult growth hormone deficiency (AGHD)[4-6], increased number of studies have shown that stroke and other acute brain injuries[7], including traumatic brain injury (TBI) and subarachnoid hemorrhage, are among the etiologies of AGHD[8,9].

GH replacement therapy (GHRT) has been in clinical use for three decades[10] and has been reported to normalize AGHD-related signs and symptoms, including depression, anxiety, fatigue, lack of strength, and altered body composition[9]. Benefits such as improved voluntary physical activity and quality of life[9,10], increased lean body mass, reduced fat mass[11,12], and improved lipid profile[13] have been demonstrated in patients receiving GHRT. Nevertheless, other than improvements in body composition, the beneficial effects of GHRT in AGHD patients are mainly inconclusive. Moreover, studies regarding GHRT for patients suffering from ICH are scarce. Herein, we report a female patient who was diagnosed with AGHD five years after the event of ICH occurred. It is encouraging that her cognitive function, fluency of speech, and mobility drastically improved after six months of GHRT. The results of body composition, serum insulin-like growth factor-1 (IGF-1) level, and lipid profiles were also presented.

**CASE PRESENTATION**

**Chief complaints**

In late 2017, a 61-year-old female patient visited the clinic for regular follow-up. The patient’s consciousness was clear, but with dullness and impaired cognitive function.

**History of present illness**

In 2013, the patient was brought to the emergency department after losing control of her bike because of sudden-onset right-sided limb weakness. The physical...
examination revealed a Glasgow coma scale (GCS) of nine (E3M5V1). Brain computed tomography showed left putaminal intracranial hemorrhage, intraventricular hemorrhage, and hydrocephalus. Following surgical interventions, the patient (GCS of 14 [E4M6V4]) was discharged and transferred to another hospital for rehabilitation. In the following four years, the patient continuously received intensive rehabilitation therapy. Although her deep tendon reflex increased during follow-up, the patient's right-sided hemiparesis remained and continuously affected her right dominant side.

**History of past illness**
The patient had a history of hypertension and hyperglyceridemia.

**Physical examination**
The patient's physical examination revealed no remarkable findings.

**Laboratory examinations**
The glucagon stimulation test showed a significantly reduced GH (< 3 μg/L).

**FINAL DIAGNOSIS**
The patient was diagnosed with GHD, as examined with the glucagon stimulation test.

**TREATMENT**
In early 2018, the patient started a 6-mo GHRT. Subcutaneous administration of recombinant human growth hormones (rhGH) was initiated at a daily dose of 0.3 mg through an electronic injection device. During the 6-mo treatment period, the dose was increased stepwise to 1.0 mg/d (Figure 1A). According to the data retrieved from the electronic device, the patient received a full 100% of the recommended dosage. Her serum IGF-1 level gradually increased in response to rhGH administration (Figure 1A). No undesirable adverse effects were observed during the treatment period.

**OUTCOME AND FOLLOW-UP**
In line with the previous studies, the results of dual-energy X-ray absorptiometry showed that GHRT substantially improved her body composition, as lean body mass increased from 37.5 to 40.5 kg and fat mass reduced from 28.6 to 24.8 kg (Table 1 and Figure 1B). The percentage of body fat also decreased from 43.3% to 38.0% (Table 1). The lipid profile during the 6-mo treatment period is displayed in Figure 1A.

Before starting GHRT, the patient could not stand up, walk, or turn her body around without assistance due to right-sided limb weakness. She scored 14 on the GCS and 16 on the Mini-Mental State Examination (MMSE), accompanied by symptoms of disorientation, incoherent speech, and difficulty in making full sentences. Nevertheless, after six months of treatment, the patient was able to stand up and walk without any help. She could also turn her body around in approximately 6 s. At the end of treatment, the patient had a GCS of 15 and an MMSE of 22; the latter suggested a substantial improvement in cognitive function. Although the pentagon copying tasks were both scored zero before and after 6-mo GHRT, the right-hand tremor significantly improved posttreatment (Figure 2). Her speech was much more fluent, with good and positive responses to physicians' and her family's talk.

**DISCUSSION**
In the present report, a female patient who suffered ICH was diagnosed with AGHD five years later. Improvements in cognitive function, fluency of speech, and mobility were observed after six months of rhGH treatment. To the best of our knowledge, there is no case report presenting the effects of GHRT on physiological functions in patients with AGHD caused by ICH.

The beneficial effects of GHRT on body compositions are well established in
randomized controlled trials\textsuperscript{[14]}. A mean increase of 2-5.5 kg in lean body mass and a mean reduction of 4-6 kg in fat mass has been shown in previous literature\textsuperscript{[14]}. With respect to serum lipid profile, Florakis \textit{et al.}\textsuperscript{[15]} found that significant reductions in total and low-density lipoprotein-cholesterol (LDL-C) levels were observed at 6 mo of GH treatment, whereas an increment in high-density lipoprotein-cholesterol (HDL-C) level became evident at 18 mo and no significant changes were observed for triglycerides (TG) at all time points. Another study conducted by Feldt-Rasmussen \textit{et al.}\textsuperscript{[13]} also reported that serum total cholesterol (TC) and LDL-C reduced significantly upon 12-mo GH treatment, and no significant alterations in HDL-C or TG were seen. In line with previous studies, the patient in this report showed that treatment of GH resulted in an increase in lean body mass, a reduction in fat mass, and slight declines in TC and LDL-C. Nevertheless, a gradual decrease in HDL-C and fluctuations in TG were noted during the 6-month treatment period. Because the patient had a medical history of hyperglyceridemia, it is not clear whether the HDL-C and TG levels were also affected by the patient’s comorbidity.

The literature concerning the prevalence of pituitary dysfunction or GHD following stroke is scarce. According to a prospective study conducted by Bondanelli \textit{et al.}\textsuperscript{[16]}, 30.3\% and 35.4\% of the patients were found to have GHD at 1-3 mo and 12-15 mo after an ischemic stroke, respectively. A recent study reported that 7 out of 13 patients fulfilling the criteria of GHD when tested within a week post-stroke\textsuperscript{[17]}. Apart from the studies related to stroke, accumulating studies have also suggested that both TBI and subarachnoid hemorrhage are conditions at high risk of acquired GHD\textsuperscript{[18]}. Impaired pituitary function was found in about one-fifth of patients after TBI, and in 5\%-8\% GHD was identified\textsuperscript{[19,20]}. Although the association between GHD and nontraumatic ICH is still unclear, it would be expected that patients with nontraumatic ICH were also at risk of developing GHD. Owing to the lack of routine examination of pituitary hormones for patients who experienced cerebrovascular events, GHD may be unrecognized, and the patients remained unaware of their conditions unless further clinical manifestations appear months or years later. Thus, the incidence or prevalence of GHD due to cerebrovascular events could be largely underestimated.

Cognitive impairment is among the complaints reported by patients with GHD, particularly memory difficulties\textsuperscript{[21,22]}. In addition, GHD was also associated with attention and verbal memory disorders after TBI\textsuperscript{[13]}. The impact of GHRT on cognitive functions has been assessed with various performance tests but with inconsistent results. While some studies indicated that administration of GH help recovery of cognitive functions, as examined by means like verbal memory tests or neuroimaging\textsuperscript{[23-26]}, significant changes were not found in several other studies\textsuperscript{[27,28]}. In our case, the patient’s cognitive impairment was evaluated with MMSE before and after a 6-mo GH treatment. A difference of 6 points was observed between the two evaluations. The results are consistent with Devesa \textit{et al.}\textsuperscript{[29]} report that cognitive impairments were mitigated following GHRT in patients with GHD caused by TBI, as reflected by improvements in MMSE scores\textsuperscript{[29]}. These findings suggest that GHRT may provide beneficial effects for AGHD patients with cognitive impairments.

| Table 1 Body compositions |
|----------------------------|
|                            |
| Pretreatment                |
| Posttreatment               |
| Change from pretreatment    |
| Lean body mass (kg)         | 37.5 | 40.5 | +3.0 |
| Fat mass (kg)               | 28.6 | 24.8 | -3.8 |
| Fat (%)                     | 43.3 | 38.0 | -5.3 |
| Weight (kg)                 | 68.0 | 67.0 | -1.0 |
| BMI (kg/m\textsuperscript{2}) | 29.0 | 28.6 | -0.4 |
| Fat mass/Height\textsuperscript{2} | 12.2 | 10.6 | -1.6 |
| Lean/Height\textsuperscript{2} | 15.2 | 16.5 | +1.3 |
| Est. VAT mass (g)           | 796  | 630  | -136 |
| Est. VAT volume (cm\textsuperscript{3}) | 861  | 681  | -180 |
| Est. VAT area (cm\textsuperscript{2}) | 165  | 131  | -34  |

BMI: Body mass index; Est. VAT: Estimated visceral adipose tissue.
Motor improvements have been previously revealed in patients receiving growth hormone treatment. In a series of TBI cases, the administration of growth hormone was initiated 2.5 mo to 11 years after TBI. Motor improvements were found in months after commencing the treatment as assessed with Functional ambulation categories and Tinetti balance and gait tests in both GHD and non-GHD patients[29]. In our case, the patient received GHRT five years after ICH and was able to stand up and walk without assistance following the treatment. In addition to the neurotrophic effects of GH[30], the improved body composition and enhanced muscle strength may also contribute to the patient’s motivation to leave her bed.

During the entire 6-month treatment period, IGF-1 Levels were checked every month to monitor the patient’s response to dose changes over time. The IGF-1
concentration increased from 178 ng/mL before the treatment to 390 ng/mL at the end of treatment. In healthy female Chinese adults aged 60-64 years, the 2.5 and 97.5 percentile values for serum IGF-1 are 46.5 and 210.4, respectively\[^{31}\]. Because no unfavorable side effects were shown and the improvements in mobility and neurological symptoms emerged, the dosage of rhGH at 1 mg/d (a dosage within the recommended range of locally approved prescribing information) was maintained with close monitoring for the last two months, and the treatment was planned to be stopped afterward. The case showed a substantial improvement in MMSE while having an elevated IGF-1 Level. Low serum IGF-1 Levels were reported to be independently associated with unfavorable functional outcome and death in patients with ischemic stroke\[^{32}\]. Nevertheless, the association between IGF-1 and cognitive performance is still controversial. In elderly subjects, it was previously shown that circulating IGF-I may be positively associated with certain cognitive functions\[^{33,34}\], despite that an inverse relationship between IGF-1 Level and cognitive performance was also reported\[^{35}\]. Thus, whether IGF-1 was positively related to cognitive function requires future studies for further elucidation.

**CONCLUSION**

Although it is not known whether the ameliorations in cognition or motor performance could be directly attributable to GH treatment for the present case, the improvements following GHRT is prominent and encouraging, suggesting cognitive and motor impairments of ICH patients may be partially reversed by growth hormone treatment. Current evidence regarding the beneficial effects of GHRT on cognitive and motor function remains limited. Without severe loss of neurological function, the effects may be too subtle to be detected in the general AGHD patients. Therefore, to further confirm whether GH treatment can reverse cognitive deterioration and neurological sequelae cerebrovascular events, randomized controlled studies in the cohorts of ICH or TBI are needed.

**ACKNOWLEDGEMENTS**

Medical writing assistance was funded by Merck Ltd., the funder did not have any roles in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**REFERENCES**

1. Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstine R, Chou D, Delavalle R, Danaei G, Ezzati M, Fahimi A, Flaxman D, Foreman, Gabriel S, Gakidou E, Kassebaum N, Khlatibzadeh S, Lim S, Lipshultz SE,
Liu JT et al. Neurological improvements following GHRT

London S, Lopez, MacIntyre MF, Mokdad AH, Moran A, Moran AE, Mozaffarian D, Murphy T, Naghavi M, Pope C, Roberts T, Salomeon J, Schwabe DC, Shahraz S, Sleet DA, Murray, Abraham J, Ali MK, Atkinson C, Bartels DH, Bhalla K, Birbeck G, Burstein R, Chen H, Crispi MH, Dahodwala, Jafars, Ding EL, Dorsey ER, Ebel BE, Ezzati M, Fattah, Flaxman S, Flaxman AD, Gonzalez-Medina D, Grant B, Hagan H, Hoffmann H, Kassebaum N, Khazdahbzed S, Leasher JL, Lin J, Lipshultz SE, Lozano R, Lu Y, Mallinger L, McDermott MM, Micha R, Miller TR, Mokdad AA, Mokdad AH, Mozaffarian D, Naghavi M, Narayan KM, Omer SB, Pelizzi PM, Phillips D, Ranganathan D, Rivara FP, Roberts T, Sampson U, Sanman E, Sapkota A, Schwabe DC, Sharaz S, Shivakoti R, Singh GM, Singh D, Tavakkoli M, Towbin JA, Wilkinson JD, Zabetian A, Murray, Abraham J, Ali MK, Alvarado M, Atkinson C, Badoud LM, Benjamin EJ, Bhalla K, Birbeck G, Bolliger I, Burstein R, Caranahm E, Chou D, Chugh SS, Cohen A, Colson KE, Cooper TL, Couser W, Crispi MH, Dabhadkar KC, Delvalle RP, Jafars, Dicker D, Dorsey ER, Dubet H, Ebel BE, Engell RE, Ezzati M, Ezelion DT, Finucane MM, Flaxman S, Flaxman AD, Fleming T, Foreman, Foretsov, Fung MH, Freedman G, Freeman MK, Gakidou E, Gilmah RF, Gonzalez-Medina D, Gosselin R, Gutierrez HR, Hagan H, Haverkollmer R, Hoffmann H, Jacobsen KH, James SL, Jasrasaria R, Jayramn S, Johns N, Kassebaum N, Khatib, Khazdahzed S, Lan Q, Leasher JL, Lim S, Lipshultz SE, London S, Lopez, Lozano R, Lu Y, Mallinger L, Meltozer M, Mensah GA, Michaud C, Miller TR, Mock C, Moffitt TE, Mokdad AA, Mokdad AH, Moran A, Naghavi M, Narayan KM, Nelson NG, Olives C, Omer SB, Orlbalt K, Ostro B, Pelizzi PM, Phillips D, Raju M, Razavi H, Ritz B, Roberts T, Sacco RL, Salomeon J, Sampson U, Schwabe DC, Shahraz S, Shibuya K, Silverberg D, Singh JA, Steenland K, Taylor JA, Thurston GD, Yavallya MS, Vos T, Wagner GR, Weirnstock MA, Weisskopf MG, Wall S, Murray, U. S. Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA 2013; 310: 591-608 [PMID: 23842577 DOI: 10.1001/jama.2013.13805]

2 Aguilar MI, Brott TG. Update in intracerebral hemorrhage. Neurohospitalist 2011; 1: 148-159 [PMID: 23988350 DOI: 10.1177/1941875211409050]

3 Gupta V. Adult growth hormone deficiency. Indian J Endocrinol Metab 2011; 15 Suppl 3: S197-S202 [PMID: 22029024 DOI: 10.4103/2230-8210.84865]

4 Stockholn K, Gravholt CH, Laursen T, Jorgensen JO, Laurberg P, Andersen M, Kristensen L0, Feldt-Rasmussen U, Christiansen JS, Frydenberg M, Green A. Incidence of GH deficiency - a nationwide study. Eur J Endocrinol 2006; 155: 61-71 [PMID: 16793951 DOI: 10.1530/eje.1.02191]

5 Abs R, Bengilson BA, Hernberg-Stohle E, Monson JP, Tauber JP, Wilson P, Wüster C. GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. Clin Endocrinol (Oxf) 1999; 50: 703-711 [PMID: 10468941 DOI: 10.1046/j.1365-2265.1999.00605.x]

6 Bouj HA, Gaykema WDC, Kuijpers KAJ, Pouwels MM, den Hertog HM. Pituitary dysfunction and association with fatigue in stroke and other acute brain injury. Endocr Connect 2018; 7: R223-R237 [PMID: 29748174 DOI: 10.1530/EC-18-0147]

7 Kargi AY, Merriam GR. Diagnosis and treatment of growth hormone deficiency in adults. Nat Rev Endocrinol 2013; 9: 335-345 [PMID: 23629539 DOI: 10.1038/nrendo.2013.77]

8 Allen DB, Backeljauw P, Bidlingmaier M, Biller BM, Boguszewski M, Burman P, Butler G, Chihara K, Christiansen J, Citaranani S, Clayton P, Clemmens D, Cohen P, Darendeliler F, Deal C, Dunger D, Erfurth EL, Dorsey ER, Ebel BE, Engell RE, Ezzati M, Ezelion DT, Finucane MM, Flaxman S, Flaxman AD, Fleming T, Foreman, Foretsov, Fung MH, Freedman G, Freeman MK, Gakidou E, Gilmah RF, Gonzalez-Medina D, Gosselin R, Gutierrez HR, Hagan H, Haverkollmer R, Hoffmann H, Jacobsen KH, James SL, Jasrasaria R, Jayramn S, Johns N, Kassebaum N, Khatib, Khazdahzed S, Lan Q, Leasher JL, Lim S, Lipshultz SE, London S, Lopez, Lozano R, Lu Y, Mallinger L, Meltozer M, Mensah GA, Michaud C, Miller TR, Mock C, Moffitt TE, Mokdad AA, Mokdad AH, Moran A, Naghavi M, Narayan KM, Nelson NG, Olives C, Omer SB, Orlbalt K, Ostro B, Pelizzi PM, Phillips D, Raju M, Razavi H, Ritz B, Roberts T, Sacco RL, Salomeon J, Sampson U, Schwabe DC, Shahraz S, Shibuya K, Silverberg D, Singh JA, Steenland K, Taylor JA, Thurston GD, Yavallya MS, Vos T, Wagner GR, Weirnstock MA, Weisskopf MG, Wall S, Murray, U. S. Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA 2013; 310: 591-608 [PMID: 23842577 DOI: 10.1001/jama.2013.13805]
Liu JT et al. Neurological improvements following GHRT

17 Lillicrap T, Garcia-Esporon C, Walker FR, Ong LK, Nilsson M, Spratt N, Levi CR, Parsons M, Isagaard J, Bivard A. Growth Hormone Deficiency Is Frequent After Recent Stroke. Front Neurol 2018; 9: 713 [PMID: 30237782 DOI: 10.3389/fneur.2018.00713]

18 Aimaretti G, Ambrosio MR, Di Somma C, Fisso C, Cannavo S, Gasperti M, Scaroni C, De Marinis L, Benvena S, degli Uberti EC, Lombardi G, Mantero F, Martino E, Giordano G, Ghigo E. Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. Clin Endocrinol (Oxf) 2004; 61: 320-326 [PMID: 15355447 DOI: 10.1111/j.1365-2265.2004.02094.x]

19 Herrmann BL, Rehder J, Kahlke S, Wiedemann H, Doerfler A, Ischebeck W, Laumer R, Forsting M, Stoilke D, Mann K. Hypopituitarism following severe traumatic brain injury. Exp Clin Endocrinol Diabetes 2006; 114: 316-321 [PMID: 16868899 DOI: 10.1055/s-2006-924254]

20 Berg C, Oelffer A, Schaum-Draeger PM, Bodor F, Braband G, Gerbert B, Bornstein S, Zimmermann A, Weber M, Broecker-Preuss M, Mann K, Herrmann BL. Prevalence of anterior pituitary dysfunction in patients following traumatic brain injury in a German multi-centre screening program. Exp Clin Endocrinol Diabetes 2010; 118: 139-144 [PMID: 19691014 DOI: 10.1055/s-0029-1225611]

21 Bengtsson BA, Edén S, Lönn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tölli J, Sjöström L, Isaksson OG. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J Clin Endocrinol Metab 1993; 76: 309-317 [PMID: 8432773 DOI: 10.1210/jcem.76.2.8432773]

22 Deijen JB, de Boer H, Blok GJ, van der Veen EA. Cognitive impairments and mood disturbances in growth hormone deficient men. Psychoneuroendocrinology 1996; 21: 313-322 [PMID: 8817729 DOI: 10.1016/0306-4530(95)00050-x]

23 Kozlowski Moreau O, Yollin E, Merlen E, Daveluy W, Rousseaux M. Lasting pituitary hormone deficiency after traumatic brain injury. J Neurotrauma 2012; 29: 81-89 [PMID: 21992034 DOI: 10.1089/neu.2011.2048]

24 Arwert LI, Veltman DJ, Deijen JB, van Dam PS, Drent ML. Effects of growth hormone substitution therapy on cognitive functioning in growth hormone deficient patients: a functional MRI study. Neuroendocrinology 2006; 83: 12-19 [PMID: 16707911 DOI: 10.1159/000093337]

25 Moreau OK, Cortet-Radulelli C, Yollin E, Merlen E, Daveluy W, Rousseaux M. Growth hormone replacement therapy in patients with traumatic brain injury. J Neurotrauma 2013; 30: 998-1006 [PMID: 23323993 DOI: 10.1089/neu.2012.2705]

26 Marie NP, Doknic M, Pavlovic D, Pekic S, Stojanovic M, Jasovic-Gasic M, Popovic V. Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy. J Endocrinol Invest 2010; 33: 770-775 [PMID: 20479560 DOI: 10.1007/BF03530430]

27 Oertel H, Schneider HJ, Stallia GK, Holbober F, Zühl J. The effect of chronic growth hormone substitution on cognitive performance in adult patients with hypopituitarism. Psychoneuroendocrinology 2004; 29: 839-850 [PMID: 15177699 DOI: 10.1016/j.psyneuen.2003.05.015]

28 Mossberg KA, Durham WJ, Zgaljardic DJ, Gilkinson CR, Danesi CP, Sheffield-Moore M, Masel BE, Urban RJ. Functional Changes after Recombinant Human Growth Hormone Replacement in Patients with Chronic Traumatic Brain Injury and Abnormal Growth Hormone Secretion. J Neurotrauma 2017; 34: 845-852 [PMID: 27627580 DOI: 10.1089/neu.2016.4552]

29 Devesa J, Reimunde P, Devesa P, Barberá M, Arce V. Growth hormone (GH) and brain trauma. Horm Behav 2013; 63: 331-344 [PMID: 22405763 DOI: 10.1016/j.yhbeh.2012.02.022]

30 Martinez-Moreno CG, Calderón-Vallío D, Harvey S, Arámbaro C, Quintanar JL. Growth hormone (GH) and Gonadotropin-Releasing Hormone (GnRH) in the Central Nervous System: A Potential Neurological Combinatory Therapy? Int J Mol Sci 2018; 19 [PMID: 29375545 DOI: 10.3390/ijms19020377]

31 Zhu H, Xu Y, Gong F, Shan G, Yang H, Xu K, Zhang D, Cheng X, Zhang Z, Chen S, Wang L, Pan H. Reference ranges for serum insulin-like growth factor I (IGF-I) in healthy Chinese adults. PLoS One 2017; 12: e0185561 [PMID: 28976993 DOI: 10.1371/journal.pone.0185561]

32 Tang JH, Ma LL, Yu TX, Zheng J, Zhang HJ, Liang H, Shao P. Insulin-like growth factor-I as a prognostic marker in patients with acute ischemic stroke. PLoS One 2014; 9: e99186 [PMID: 24911265 DOI: 10.1371/journal.pone.0099186]

33 Aleman A, Verhaar HJ, De Haan EH, De Vries WR, Sammon MS, Drent ML, Van der Veen EA, Koppeschaar HP. Insulin-like growth factor-I and cognitive function in healthy older men. J Clin Endocrinol Metab 1999; 84: 471-475 [PMID: 10022403 DOI: 10.1210/jcem.84.2.4545]

34 Wennberg AMV, Hagen CE, Machulda MM, Hollman JH, Roberts RO, Knopman DS, Petersen RC, Mielke MM. The association between peripheral total IGF-1, IGFBP-3, and IGF-1/IGFBP-3 and functional and cognitive outcomes in the Mayo Clinic Study of Aging. Neurobiol Aging 2018; 66: 68-74 [PMID: 29547749 DOI: 10.1016/j.neurobiolaging.2017.11.017]

35 van Bunderen CC, Deijen JB, Drent ML. Effect of low-normal and high-normal IGF-1 levels on memory and wellbeing during growth hormone replacement therapy: a randomized clinical trial in adult growth hormone deficiency. Health Qual Life Outcomes 2018; 16: 135 [PMID: 29980224 DOI: 10.1186/s12955-018-0963-2]
