Growth Hormone & IGF Research 25 (2015) 269–273

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Serum IGF-1 is higher in patients with idiopathic normal pressure hydrocephalus than in the population

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ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form 21 September 2015
Accepted 17 October 2015
Available online 17 October 2015

Keywords:
IGF-1
Pituitary hormones
Sex hormones
Normal pressure hydrocephalus

ABSTRACT

Background: Hypopituitarism has been reported in patients with idiopathic normal pressure hydrocephalus (iNPH), which could enhance characteristic symptoms like impaired wakefulness, gait, body balance, and subcortical cognitive deterioration.
Purpose: To compare basal serum levels of pituitary and sex hormones and serum insulin-like growth factor-1 (S-IGF-1) in patients with iNPH and an age-matched control population, and to correlate the preoperative hormone levels with symptoms and signs pre-operatively and three months after surgery.
Methods: A cross-sectional case control design was used. Patients diagnosed with iNPH, n = 108 (65 men and 43 women, mean age 72.3 years), were consecutively included during 2006–2011 at Sahlgrenska University Hospital, Gothenburg, Sweden. S-TSH, S-free T4, S-FSH, S-LH, S-prolactin, plasma ACTH, S-testosterone, S-oestradiol and S-IGF-1 were examined. Symptoms and signs were scored using the iNPH scale score. Population controls, n = 146, were recruited from the WHO MONICA project, Gothenburg in 2008.
Results: Men and women with iNPH had higher S-IGF-1 than controls ($p < 0.001$). Women with iNPH had lower S-TSH ($p = 0.016$) than controls, but the frequency of levothyroxine substitution was similar. Among men, a higher level of S-IGF-1 was associated with milder symptoms, while higher levels of S-FSH and S-LH were associated with more severe symptoms.
Conclusions: Patients with iNPH did not have lower levels of pituitary or sex hormones but presented with higher levels of S-IGF-1, compared with healthy, age-matched controls. Higher S-IGF-1 in men was related to milder mental and physical symptoms and signs.

1. Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is often caused by impaired absorption of cerebrospinal fluid (CSF), producing a widening of all ventricles including the third ventricle. The intracranial pressure (ICP) is within normal ranges and there is free communication between the ventricles and the subarachnoid space [1]. The symptomatology is gait and balance disturbances, cognitive impairment and uninhibited bladder [2]. The disorder is treatable by ventriculoperitoneal or ventriculo-atrial shunting and the outcome is good in around 80% of iNPH patients [3,4].

Stagnation of extracellular fluid, reduced metabolism and impaired perfusion in the periventricular tissue have recently been suggested as possible pathophysiological mechanisms in iNPH [5–7]. Third ventricle adjacent structures and connected structures, like the anterior cingulate cortex, are considered related to symptoms and signs [8–11].

Hypothalamo-hypophyseal insufficiency in iNPH patients was reported by Barber and Garvan [12]. Moin et al. found pituitary dysfunction in 31% of iNPH patients, most commonly hypogonadism [13]. In children with hydrocephalus, higher body mass index (BMI) and body fat mass, lower insulin-like growth factor I (IGF-I) levels, and impaired growth hormone (GH) responses on dynamic testing, were reported [14]. The GH/IGF-I axis has been considered to be involved in the regulation of brain growth, development and myelination [15]. GH, and particularly IGF-I, have been ascribed neuroprotective effects [16,17].

The aims of this study were to 1) explore whether basal pituitary and sex hormone and S-IGF-1 levels were lower in subjects with iNPH than in age-matched controls, by analysing serum levels of thyroid-stimulating hormone (TSH), free thyroxine (T4), prolactin, follicle-

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http://dx.doi.org/10.1016/j.ghir.2015.10.001
1096-6374/

stimulating hormone (FSH), luteinising hormone (LH), testosterone, oestradiol, adrenocorticotropic hormone (ACTH) and IGF-1, and 2) to correlate the preoperative hormone levels among iNPH patients with symptoms and signs before and three months after surgery.

2. Materials and methods

2.1. Patients

The study included 108 patients consecutively diagnosed with iNPH during the years 2006–2011. Four patients were excluded due to lack of blood samples. Serum from 104 patients, 62 men and 42 women (mean age 72.3 ± 8.4 years, range 48–89), could be analysed (Table 1).

The patients were diagnosed as probable iNPH according to the American-European guidelines [2]. The patients were examined before and three months after surgery, and the clinical outcome was scored using the iNPH scale [18]. The iNPH scale score is the weighted mean score of assessments in the four domains of gait, neuropsychology, balance (static) and continence. The total iNPH scale score and the separate domain scores have a min.–max. range from 0 to 100, where 100 represents normal performance among healthy individuals in an iNPH typical age range of 70–74 years. An increase in the score of ≥5 points was categorised as a good outcome and <5 points as a poor outcome. Body weight and height were measured without shoes and BMI was calculated as body weight (kg) divided by height (m) squared and expressed as kg/m^2. All patients were operated upon using an adjustable ventriculoperitoneal shunt (PS Medical Strata®, Medtronic Inc., Goleta, CA, USA or Codman & Schurtleff/Johnson & Johnson Co., Raynham, MA).

The medical records of the 104 patients were scrutinised for any on-going medication related to hormonal function. If present, the patient was excluded from the relevant hormone analysis.

2.2. Control population

A random population sample of 1200 men and 1200 women were recruited from the **WHO MONICA** population study (**W**orld **H**ealth **O**rganization **MONI**toring of trends and determinants for **CA**rdiovascular disease project, Gothenburg, Sweden). The participation rate was 67%, n = 1616, in 1995. Hormonal analyses were performed in one in four of the participating men and women 25–64 years of age, and in all the women in the age group 45–64 years; 608 subjects in total. The subjects were invited for the re-evaluation in 2007–2008 where 410 subjects participated (67% participation rate). Age-matched subjects from 2008 were chosen for our reference population; 146 subjects 25 men and 121 women, in total (Table 1).

Blood samples were collected after an overnight fast. Similar methods for anthropometry and the same biochemical methods as for the patients were used, except for serum prolactin and plasma ACTH, which were not analysed in the controls.

On-going pharmacological treatments among the WHO MONICA subjects were documented via questionnaires and coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.

Table 1
Age and body mass index (BMI) of the patients with idiopathic normal pressure hydrocephalus (iNPH) and controls from the WHO MONICA study. There were no significant differences in age or BMI between patients and controls, respectively.

		Age, years			BMI, kg/m^2		
		Mean ± SD	Range	N	Mean ± SD	Range	N
iNPH	Men	72 ± 10	48–89	62	26 ± 3	21–34	62
	Women	73 ± 6	62–87	42	27 ± 5	19–41	39
	Total	72 ± 8	48–89	104	26 ± 4	19–41	101
WHO MONICA	Men	72 ± 3	68–77	25	27 ± 3	22–33	25
	Women	72 ± 3	68–78	121	27 ± 5	17–50	121
	Total	72 ± 3	68–78	146	27 ± 5	17–50	146

2.3. Blood samples

All blood samples were drawn from the patients pre-operatively after fasting and avoiding nicotine use for 4 h. The tests were analysed at the Laboratory for Clinical Chemistry at Sahlgrenska University Hospital, Gothenburg, Sweden. The following substances were measured in serum (S) and plasma (P): free T4, TSH, prolactin, FSH, LH, testosterone, oestradiol, ACTH and IGF-1. S-prolactin and P-ACTH were not analysed among the controls. For this reason, the patients' results were instead compared with the reference values provided by the laboratory.

S-free T4 and S-TSH were measured with the ECLIA immunometric method, Roche. S-FSH and S-LH were measured with chemiluminescent microparticle immunoassays from Abbott Architect (Abbott Laboratories, Abbott Park, IL, USA). S-IGF-1 was measured with Siemens Immulite (Siemens Medical Solutions, Los Angeles, CA, USA).

Before September 1, 2008, serum total testosterone was measured by Siemens Centaur, and after 2008 by Beckman Coulter Access Immunoassay Systems (Beckman Coulter, Inc., Fullerton, CA). The new method was 13% higher at concentrations ≤12 nmol/L and 6% higher at concentrations >12 nmol/L. The functional sensitivity was 1 nmol/L. Only the converted values are shown in the results.

Before November 26, 2009, S-oestradiol was measured by radioimmunoassay (RIA), DiaSorin, and, after that date, by Abbott Architect. The new method was 25% higher at concentrations <300 pmol/L, which was the case in all patients due to their high age. The functional sensitivity was 50 pmol/L. Only the converted values are shown in the results.

2.4. Statistical analysis

Mean values, standard deviations (SD), t-tests and chi-square tests were calculated using conventional methods in Microsoft Excel. Spearman's correlations were calculated in IBM SPSS 17.0 (IBM, Armonk, NY, USA) for Windows. No Bonferroni correction for multiple correlation analyses was made due to explorative character of the study. The between-group comparison of hormones was adjusted for age and BMI.

2.5. Ethics

This study has been approved by the Ethics Committee at the University of Gothenburg, registration numbers 154–05 and 088–06. All subjects from the WHO MONICA project gave their written informed consent to the study. The study complies with the Declaration of Helsinki.

3. Results

There was no difference in mean age or BMI between patients with iNPH and controls (Table 1). Ninety-one of the 104 iNPH patients could be re-evaluated three months after surgery; 13 were lost to follow-up or had incomplete data. Fifty-nine patients (65%) improved, 15% were unchanged and 20% had deteriorated in their symptom scores.

Nine women (21%) with iNPH used levothyroxine, versus 18 (15%) in the control population (p = 0.325, data not shown) mainly due to primary hypothyroidism in both groups.

Two men with iNPH were treated with testosterone supplementation. One woman with iNPH was treated with oestrogen hormone replacement therapy (HRT). Nine women among the controls had HRT.

There was no difference between the groups regarding medical therapy (data not shown).