

Hypopituitarism in the Elderly: Multifaceted Clinical and Biochemical Presentation

L. Foppiani^{*1}, A. Ruelle², R. Bandelloni³, P. Quilici³ and P. Del Monte¹

¹Endocrinology, ²Division of Neurosurgery, ³Unit of Pathology, Galliera Hospital, Genova, Italy

Abstract: Hypopituitarism (HYPO) is a rare and under-investigated pathology in the elderly.

Aim: to review our case records of patients ≥ 65 yrs with first diagnosis of anterior global hypopituitarism, in order to evaluate presentation symptoms, etiology, biochemical and hormonal pictures, pituitary morphology, and efficacy of therapy.

Patients: 15 patients (65-82 yrs) were studied: in 11 (73%) HYPO was secondary to pituitary macroadenoma (non-secreting in 10 and GH-secreting in 1); in 3 it was associated to empty sella, and in 1 to pituitary hypoplasia.

Results: major presenting symptoms were visual-field defects and asthenia (40%) but also memory and/or gait impairment and nausea (30%) and depression (20%) were significantly observed. Dyslipidemia (73%), anemia (20%) and severe hyponatremia (13%) were found. After starting substitutive therapy and clinical improvement, 10 patients with macroadenoma underwent uneventful neurosurgery, which improved visual alterations but not pituitary function. Immunohistochemistry showed positivity for FSH in one patient and for GH in one patient. Six out of the eight patients with a post-surgical tumor remnant required treatment (surgery/radiotherapy/somatostatin analogue treatment in the acromegalic patient).

Conclusions: The diagnosis of HYPO is often delayed in the elderly, since symptoms may be ascribed to aging and associated comorbidities. In our series, most of the aspecific symptoms were retrospectively addressed to HYPO since their resolution/improvement with replacement therapy. The prevalent cause of HYPO remains non-functioning pituitary macroadenomas. Hyponatremia can be a life-threatening presenting symptom. Symptoms considered apparently aspecific in the elderly should be investigated in order to possibly diagnose an important treatable disorder as HYPO.

Keywords: Hypopituitarism, elderly, pituitary macroadenoma, empty sella, replacement therapy, neurosurgery.

INTRODUCTION

Hypopituitarism (HYPO) is an uncommon and under-investigated disease in the elderly, since its symptoms are often unspecific and can easily be ascribed to aging and related comorbidities. Nevertheless, a proper diagnosis and therapy of HYPO is of the utmost importance, as the clinical consequences of untreated disease can be severe [1-3]. A combined approach is generally required to treat HYPO. In addition, it is well known that patients with HYPO have increased mortality, particularly in the females, mostly owing to cardiovascular diseases [1-3]. Until a few years ago, the most common cause of HYPO was considered to be pituitary tumors. Nowadays, however, it has been acknowledged that brain damage of different etiologies (e.g. traumas, aneurysmal subarachnoid hemorrhage and ischemic stroke), which was formerly unascertained and therefore underestimated, is a significant cause of hypothalamic-pituitary dysfunction [1]. These pathologies usually cause partial HYPO, and mainly affect GH and gonadotropin secretion, which may recover over time in several patients [1, 4-6]. As a consequence of hormone deficiencies, HYPO can impair quality of life and cause potentially life-threatening complications such as hyponatremia, which in the elderly is usually related to aging

process, drugs or various comorbidities [7-9]. The aim of our study was to retrospectively review our case records of older (≥ 65 yrs) patients with first diagnosis of anterior global hypopituitarism, in order to evaluate presentation symptoms, etiology, biochemical and hormonal pictures, pituitary morphology and histology, and efficacy of therapy.

PATIENTS AND METHODS

Fifteen elderly patients (8M, 7 F; age range 65-82 yrs; median 70 yrs) were studied; 14 had global anterior hypopituitarism (HYPO) and one had acromegaly and partial hypopituitarism (secondary hypocortisolism and hypothyroidism and low FSH and LH levels for age). Table 1 shows the mass-related symptoms and/or heterogeneous symptoms which prompted brain morphology assessment; this was performed by means of magnetic resonance imaging (MRI), or computed tomography (CT) if MRI was contraindicated, and/or hormonal evaluation (see results section). Baseline serum pituitary (LH, FSH, PRL, TSH, ACTH) and target gland hormones (FT4, FT3, IGF-I, 17-beta estradiol, total testosterone) were determined by radioimmunologic or immunometric methods, using commercially available kits, in all patients the morning after overnight fasting. Serum total IGF-I was determined after acid-ethanol extraction of the samples, in order to avoid binding-protein interference. Routine blood chemistry was performed in all patients. All patients underwent ophthalmologic examination and visual field perimetry. In those patients who underwent neurosur-

*Address correspondence to this author at the Endocrinology, Galliera Hospital, Mura delle Cappuccine 14, 16128 Genova, Italy; Tel: 0039010/5634321; Fax: 0039010/5634306; E-mail: luca.foppiani@galliera.it

Table 1. Clinical, Biochemical and Neuroradiological Findings at Diagnosis in the Patients Studied

N°	PATIENTS	SEX	AGE	SYMPTOMS	CHEMISTRY	MRI/CT	EXTRASELLAR EXPANSION/SIDE	HORMONAL STATUS
						ADENOMA SIZE (cm)		
MACROADENOMA								
1	F.A.	M	74	incidental (head trauma)	dyslipidemia	3.0	optic chiasma-third ventricle	hypopituitarism
2	G.M.	M	70	visual field defect, dizziness, depression, nausea, vomiting	dyslipidemia	3.0	optic chiasma-sphenoidal sinus	hypopituitarism
3	M.E.	M	71	diplopy, visual field defect	dyslipidemia	2.5	optic chiasma	hypopituitarism
4	P.F.	M	72	visual field defect	-	3.5	optic chiasma-cavernous sinus	hypopituitarism
5	P.E.	M	66	visual field defect	anemia, dyslipidemia	4.0	third ventricle-optic chiasma-cavernous sinuses	hypopituitarism
6	T.A.	F	65	visual field defect	dyslipidemia	4.0	optic chiasma-cavernous sinuses-third ventricle (hydrocefalus)	hypopituitarism
7	T.M.	M	78	asthenia, hypotension, nausea, depression, memory/gait impairment	severe dyslipidemia	2.5	optic chiasma	hypopituitarism, increased PRL
8	T.G.	F	82	incidental (head trauma), memory/gait impairment	dyslipidemia	4.0	third ventricle (hydrocefalus)-optic chiasma	hypopituitarism, increased PRL
9	T.N.	F	74	asthenia, anorexia, nausea, hypotension vomiting, memory/gait impairment	hyponatremia	4.0	optic chiasma-cavernous sinuses	hypopituitarism, increased PRL

(Table 1). Contd.....

N°	PATIENTS	SEX	AGE	SYMPTOMS	CHEMISTRY	MRI/CT	EXTRASELLAR EXPANSION/SIDE	HORMONAL STATUS
10	T.A.	M	65	visual field defect, erectile dysfunction, asthenia	dyslipidemia	3.5	cavernous sinuses- rocca petrosa	hypopituitarism, increased PRL
GH-SECRETING								
MACROADENOMA								
11	F.F.	F	65	asthenia, nausea, vomiting, slight fever	-	4.5	cavernous sinuses sphenoidal sinus suprasellar cysterna	hypopituitarism (LH/FSH/TSH/ACTH)
EMPTY SELLA								
12	O.G.	M	67	dizziness, asthenia, nausea, depression, memory/gait impairment	dyslipidemia	empty sella		hypopituitarism
13	C.L.	F	65	(previous cardiac and cerebral stroke)	hyponatremia, anemia	empty sella		hypopituitarism
14	T.E.	F	74	asthenia, anorexia, edemas, memory/gait impairment	anemia, dyslipidemia	empty sella		hypopituitarism
PITUITARY HYPOPLASIA								
15	V.M.	F	66	asthenia	dyslipidemia	pituitary hypoplasia		hypopituitarism

gery for pituitary mass, pituitary function was re-evaluated after surgery and patients were scheduled for regular follow-up examinations. Histological examinations (hematoxylin-eosin stain) and immunohistochemical (immunoperoxidase method, 3,3' diaminobenzidine as chromogen) studies for the various pituitary hormones and for chromogranin-A were carried out on each surgical sample. Ki-67 assessment, as a marker of proliferative activity, was performed by means of MIB-1 antibody, and the labeling index was calculated. Pituitary MRI or CT, visual field perimetry and ophthalmologic examination were performed 6 months after the surgery, and then yearly, unless otherwise indicated.

RESULTS

Table 1 shows the multifaceted presenting symptoms that prompted brain MRI/CT and/or baseline endocrine evaluations of pituitary and target gland hormones, which were compatible with HYPO. Visual field defects were the most frequent symptoms, but other common symptoms in the elderly, such as memory and gait impairment, asthenia, depression, hypotension and nausea were also present. Apart from visual field defects which were present only in the patients with macroadenoma, we did not observe specific etiology-related symptoms.

In our case-record, notably, one patient was referred to the emergency room for the onset of coma with severe hyponatremia during a febrile illness, which was only subsequently related to HYPO (due to empty sella); the patient promptly recovered following parenteral hydrocortisone and fluid administration. In 11 out of 15 patients (73%) MRI showed a pituitary macroadenoma (maximum diameter 2.5-4.5 cm, median 3.5 cm); this finding indirectly suggests a delayed diagnosis and was associated to hydrocephalus in 2 patients. In 2 patients the macroadenoma was incidentally discovered during morphologic examination following head trauma. All tumors except one (GH-secreting) were non-functioning pituitary macroadenomas (NFPMs). Three patients showed an empty sella (ES) (more than 50% of the sella filled with CSF and pituitary gland thickness ≤ 2 mm)

and 1 patient had pituitary hypoplasia. Notably one patient with ES had previously suffered from an ischemic cerebral stroke which might have played a role in the pathogenesis of HYPO.

In all patients, serum cortisol was ≤ 2 $\mu\text{g/dl}$ and ACTH levels were < 5 pg/ml ; FT4 was reduced and FT3 was either reduced or in the low-normal range, with low or inappropriately normal TSH levels; LH and FSH were inappropriately low for age in females, whereas in males they were reduced/normal and associated with very low testosterone levels (< 1 ng/ml). Apart from the acromegalic patient, who showed increased GH: 94 ng/ml and IGF-I: 380 ng/ml (increased for age) levels, serum IGF-I levels were clearly reduced in all other patients (range 24-62 ng/ml , median 56). Five patients (33%) had hyperprolactinemia (30-143 ng/ml): this was related to stalk deviation in 4 patients and to macroprolactinemia in one patient (PRL: 143 ng/ml). None had diabetes insipidus. Interestingly, two patients came to our observation for suspected "hyperthyroidism" after isolated "suppressed" TSH levels had been found; assessment of FT4 and FT3, which proved reduced and in the low-normal range, respectively, led to the diagnosis of secondary hypothyroidism. Notably, two patients (13%), presented with severe symptomatic (one was comatose, the other one complained nausea and confusion) hyponatremia (114-116 mEq/L), which reversed after starting oral/parenteral glucocorticoid administration; this finding suggests sodium level alterations as a clue for a possible diagnosis of HYPO in the elderly. Three patients (20%) had normochromic normocytic anemia (hemoglobin range: 10.5-11.5 gr/dl) which resolved on replacement therapy. Eleven patients (73%) had dyslipidemia; 36% of these patients normalized lipid profile with replacement therapy. The clinical conditions of all patients significantly improved after starting replacement treatment (cortisone acetate/hydrocortisone, L-thyroxine). Parenteral administration of testosterone completely restored circulating testosterone levels for age (median 3.7 ng/ml) in the five compliant male patients. After careful evaluation rhGH replacement therapy was started in 3 patients and normalized age- and sex-related IGF-I levels (median 117 ng/ml).

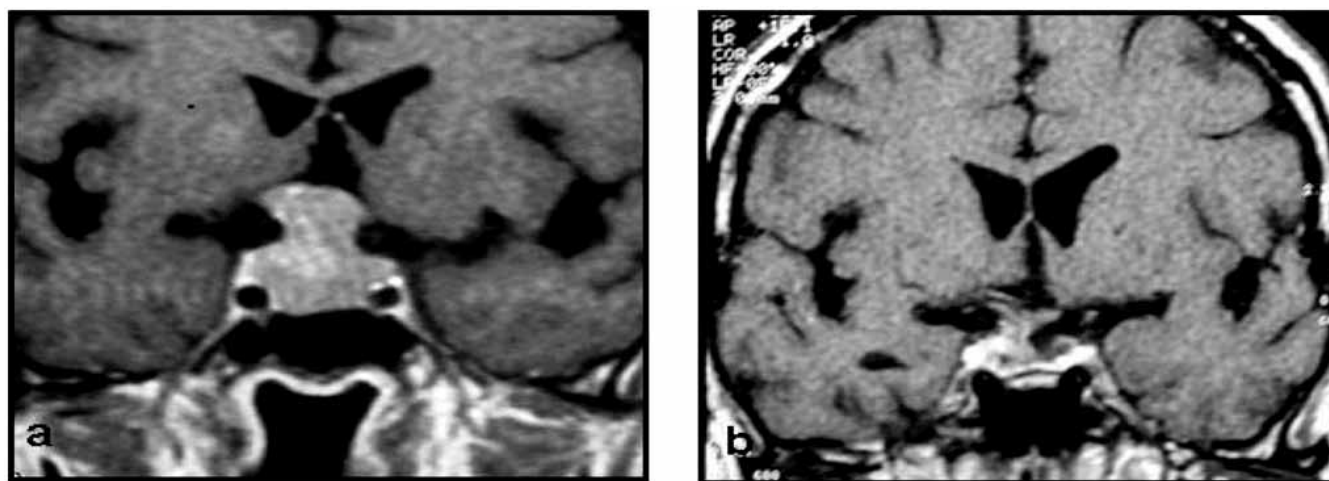


Fig. (1). Contrast-enhanced coronal T1-weighted MRI showing a large pituitary macroadenoma with suprasellar extension (patient n.5) (a). Contrast-enhanced coronal T1-weighted MRI six months after transphenoidal surgery: a small residual intrasellar tumor is evidenced.

All patients with macroadenoma, except for one who refused surgery, underwent uneventful neurosurgery (8 transphenoidal, 2 transcranial), which significantly improved/reversed visual field defects; by contrast, pituitary function did not recover in any patients (follow-up 1-10 yrs). This finding suggests a prolonged damage by the tumor to the pituitary cells. Two patients developed post-surgical transient diabetes insipidus, which was treated with desmopressin. A representative image of a large macroadenoma before and after surgery is shown in Fig. (1a, b). All resected masses were histologically compatible with pituitary adenoma (Fig. 2a). Immunohistochemistry showed positivity for FSH (Fig. 2b) in one male patient who had a large macroadenoma (which required 2 operations), and had been complaining of visual field defects for a few years. Five tumors stained for chromogranin A, and one for GH (acromegalic patient). This finding strengthens the concept that the most part of pituitary tumors which cause HYPO in the elderly are NFPM. Ki-67 assessment, as a marker of proliferative activity, was low (<3%) in all patients (Fig. 2c); this fact is a biological characteristic of pituitary adenomas, particularly in the elderly population. Eight patients (80% of

those operated on) had a post-surgical tumor remnant. Owing to the huge volume of the tumor remnant, 4 patients underwent further surgery (3 transphenoidal, 1 transcranial). Overall, 4 patients (two of those who underwent two neurosurgery operations) underwent radiotherapy (2 conventional and 2 stereotactic), which stabilized the tumor over the years. In the acromegalic patient, two surgical debulking procedures followed by radiotherapy were unable to cure the disease, but significantly improved hormonal control by somatostatin analogue. Type of treatments, hormonal and histological data and follow-up of the patients studied are shown in Table 2.

DISCUSSION

HYPO is a relatively rare and under-investigated pathology in the elderly. As far as is known, only one population-based study has evaluated the prevalence (45.5 cases per 100,000) and incidence (4.2 cases per 100,000) of HYPO in the adult population (mean age on diagnosis: 50 years; range 18-79 years), without sex differences [10]. The most frequent causes of HYPO were pituitary tumors (61%),

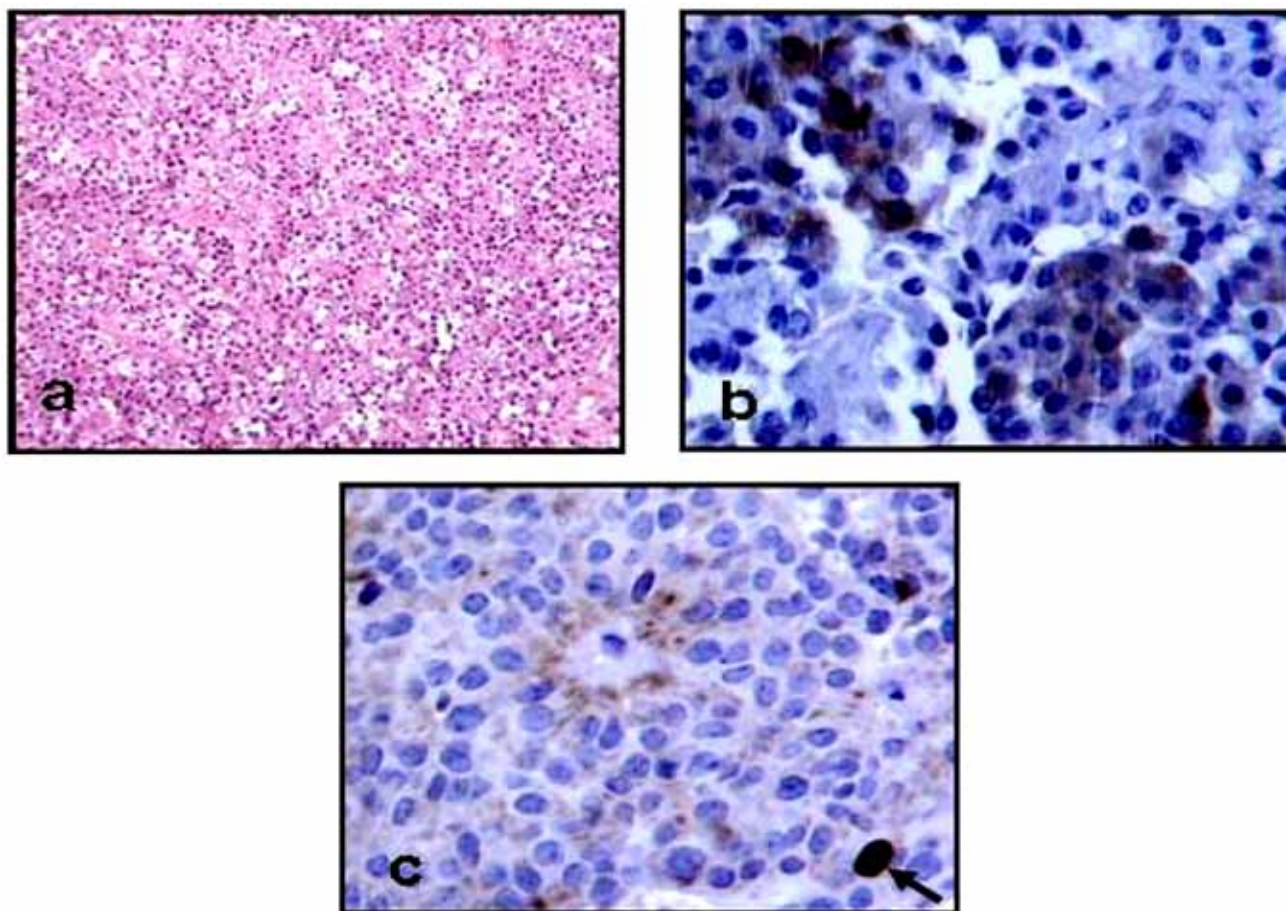


Fig. (2). Representative histological image of the pituitary adenoma is shown in Fig. (1) (patient n.5) (ematoxylin-eosin, x250) (a), immunohistochemistry for FSH (x400) (b) and for Ki-67 antigen (x400): a positive cell is shown (arrow) (c).

Table 2. Type of Treatments, Hormonal and Histological Data and Follow-Up in the Patients Studied

N°	PATIENTS	TREATMENT	POST-TREATMENT	HISTOLOGY/IHC	Ki-67 (%)	REMNANT	REGROWTH	STABLE REMNANT
NON-SECRETING								
MACROADENOMA								
1	F.A.	2 NCH	hypopituitarism	chromophobe adenoma/crg	<3	yes	no	-
2	G.M.	1 NCH	hypopituitarism	chromophobe adenoma/crg	<3	yes	no	yes
3	M.E.	1 NCH	hypopituitarism	chromophobe adenoma/crg	<3	no	no	-
4	P.F.	1 NCH	hypopituitarism	chromophobe adenoma/crg	<3	no	lost at follow-up	-
5	P.E.	2 NCH	hypopituitarism	adenoma/FSH	<3	yes	no	-
6	T.A.	2 NCH, RT	hypopituitarism	chromophobe adenoma	<3	yes	no	-
7	T.M.	refused surgery	hypopituitarism, normal PRL on therapy	-	-			
8	T.G.	1 NCH	hypopituitarism, normal PRL	chromophobe adenoma/crg	<3	yes	no	yes
9	T.N.	1 NCH, RT	hypopituitarism, normal PRL	chromophobe adenoma	<3	yes	yes	yes
10	T.A.	1 NCH, RT	hypopituitarism, normal PRL	null cell denoma	<3	yes	no	yes
GH-SECRETING								
MACROADENOMA								
11	F.F.	2 NCH, RT	hypopituitarism (LH/FSH/TSH/ACTH), normal PRL, normal GH on therapy	adenoma/GH	<3	yes	yes	yes

NCH: neurosurgery, RT: radiotherapy, crg: chromogranin A, IHC: immunohistochemistry

followed by non-tumoral causes (30%), non-pituitary lesions (9%) and empty sella (7%). Around 50% of patients had multiple pituitary hormonal deficiencies; surprisingly, LH/FSH was the most common [10].

Clinical manifestations of HYPO are multifaceted and in the elderly can easily be ascribed to the aging process, thereby preventing early proper diagnosis and therapy. The type and degree of hormonal deficiency and the rapidity of onset condition the clinical picture [1-3, 9, 11, 12]. Our study focused on a small group of elderly patients with diagnosis of global anterior hypopituitarism by different etiologies.

Our study confirms pituitary tumors (macroadenomas, mostly non-functioning) as the most prevalent (70% in our series) cause of HYPO in the elderly. These tumors are usually slowly growing and an age-related decrease in cell proliferations has been described [9]. This high prevalence is largely due to a delayed diagnosis, owing to the fact that the large majority of these tumors are NFPM (90% of our patients), which are not associated to clinical syndrome of hormonal hypersecretion, and thus patients are more likely to be diagnosed for visual-field defects (40% of our patients), incidentally (18%) or to a lesser extent by aspecific symptoms of hormonal deficiencies [9]. A delayed diagnosis leads to huge and invasive macroadenoma and prevents a radical surgery in most cases. Nevertheless, modern skillful surgery and radiotherapy are usually effective in controlling these types of tumors over the time.

Visual impairment in the elderly is usually attributed to cataracts, ischemic changes or macular degeneration, whereas pituitary diseases are rarely investigated. In addition, symptoms of hormonal defects in the old population are subtle and unspecific, particularly when they are due to empty sella/pituitary hypoplasia and therefore not associated with signs of expansive lesions. By comparing a small group of 15 younger patients with HYPO (age range 35-50 years, data non shown), we have found that the only two clinical symptoms shared with the aged HYPO group were visual field defects (also if the percentage in younger patients with macroadenoma ranged lower at 25-30% in comparison with the elderly) and asthenia, whereas the younger patients sought medical attention mostly because of symptoms of hypogonadism. Although many symptoms (asthenia, nausea, memory and gait impairment, hypotension, depression) observed in our population of elderly with HYPO are commonly found in the aged population (e.g. depression up to 30-40%, memory and gait impairment up to 30-50%) [13] the resolution/great improvement of most of them after starting hormonal replacement therapy, prompt us to address to HYPO a major role [14, 15]. In particular, the three patients who were on treatment with antidepressants withdrew the drugs shortly after starting glucocorticoid and L-thyroxine replacement. In addition, the five patients complaining of gait impairment and frequent falls significantly decreased their disability and improved their independence with replacement therapy.

The satisfactory response to hormonal therapy in our patients suggests as HYPO can be considered a potential reversible cause of neuropsychiatric disturbances in the elderly.

One of our patients, who showed clinical features of acromegaly, had a huge GH-secreting macroadenoma, with associated hyperprolactinemia due to stalk deviation, which caused HYPO. Two operations followed by radiotherapy failed to cure the disease but significantly improved the control of hormonal hypersecretion by long-acting somatostatin analogue. It is noteworthy that GH-secreting adenomas are the most common type (9-17%) of pituitary secreting adenomas in the elderly [9]. In the patients who decline surgery, or when it is contraindicated owing to severe comorbidities, chronic therapy with somatostatin analogues achieves satisfactory control of the disease in a significant percentage of patients (60-70%) and tumor shrinkage in a smaller percentage (30-40%) [9, 16]. Notably, in 3 of our patients (20%) HYPO was secondary to ES, which is the common final result of different events (vascular, autoimmune and genetic) that lead to progressive hypotrophy of the pituitary gland. In contrast with previous reports, it has recently been claimed that quite a significant percentage (up to 10%) of patients with ES have some degree of HYPO (5% with global anterior HYPO), GH deficiency being the most common defect [17, 18].

The only, albeit outstanding, life-threatening condition present in HYPO is ACTH deficiency with secondary absent or reduced cortisol production [1-3, 11, 12]. Often, baseline cortisol levels are in the low-normal range, but are unable to rise properly when stressful conditions occur. Notably, many drugs (e.g. antiepileptics, barbitures) commonly used in the elderly can increase the metabolic clearance of cortisol and further reduce its action on target tissues. The short ACTH test is useful to diagnose secondary hypocortisolism but can be "misleadingly normal" if the ACTH defect occurred recently and/or if a severely stressed, volume depleted, or hyponatremic patient is tested [19]. Tailored replacement therapy (cortisone acetate/hydrocortisone) is mandatory and enables clinical and biochemical alterations to normalize. Over-treatment must be avoided in order to prevent metabolic and bone complications. An essential point, which must be particularly strengthened in the elderly, is that patients (which must be supplied with an emergency card) must be carefully instructed with regard to stress-related dose adjustments and the possible need for parenteral administration [1-3, 11]. All our patients had very low baseline cortisol levels (≤ 2 $\mu\text{g/dl}$) which were retrospectively deemed symptomatic (asthenia, hypotension, nausea, vomiting) in roughly 50% of cases. Notably, one patient was admitted to hospital in a comatose state which was due to an undiagnosed HYPO.

A peculiar issue in the primary presenting features of HYPO in the elderly is hyponatremia, which in this particular population is usually ascribed to aging process or drugs (e.g. diuretics). Old patients are particularly prone to this hydroelectrolytic complication, which can cause neurological symptoms such as headache, nausea, disorientation, lethargy, culminating in coma. In our small series, two patients (13%) had severe symptomatic hyponatremia (114-116 mEq/L), which reversed with oral/parenteral glucocorticoid administration. Recent studies have reported that HYPO, including secondary adrenal insufficiency, is a frequently overlooked cause of hyponatremia [7, 8]. In a recent series [7], 20% of hospitalized patients with severe normovolemic

hyponatremia (mean serum sodium levels: 116 mEq/l) were suffering from previously unrecognized hypopituitarism, mostly due to empty sella (43%), Sheehan's syndrome and pituitary tumors. This abnormality is pathophysiologically based upon the inappropriate antidiuresis related both to non-suppressible arginine-vasopressin release and to a direct renal water excretion defect. Both these factors are secondary to hypocortisolism, as cortisol is a tonic inhibitor of vasopressin [7, 8, 20]. Therefore, the evaluation of serum cortisol level is strongly advisable in patients (especially elderly) with unexplained hyponatremia.

Another interesting aspect of our study is the finding of normochromic normocytic anemia in 20% of elderly patients with HYPO. Although this type of anemia is frequently found as a consequence of the aging process, in our patients HYPO surely played a prominent role, since anemia recovered in all patients on replacement therapy. The pathogenesis of anemia is based upon the deficiencies of several pituitary hormones and their target organ hormones. Glucocorticoids, thyroid hormones, androgens and GH (directly and through IGF-I) can stimulate erythropoiesis either directly or through erythropoietin stimulation [21].

The finding of central hypothyroidism at thyroid function tests can be the first clue leading to the discovery of an undiagnosed hypopituitarism in older people [12]. However, several acute and chronic illnesses can produce the same hormonal pattern and confuse matters. As for primary hypothyroidism, L-thyroxine is the treatment of choice but must be preceded by proper adrenal replacement therapy. The starting dose must be low and gradually increased over time in order to avoid subclinical/clinical hyperthyroidism, which can lead to cardiac (hyperkinetic arrhythmias) and bone complications (osteoporosis). The mean daily dose is usually lower in patients older than 60 yr ($1.3 \pm 0.2 \mu\text{g/kg bw}$) than in those younger than 60 years ($1.6 \pm 0.3 \mu\text{g/kg bw}$) [22]. Although assessed in a small sample size, our L-thyroxine replacement dose (range 0.7-1.6 $\mu\text{g/kg bw}$, median 1.1) fitted the literature data and no side effects was recorded.

Symptoms of hypogonadism are often insidious and unspecific in the elderly and are rarely complained of by the patients. Furthermore, the endocrine changes physiologically associated with aging, associated co-morbidities and drugs may confound their interpretation. Irrespective of very low testosterone levels in all our male patients, only one (13%) complained of erectile dysfunction, which resolved after testosterone replacement therapy. Apart from the sexual sphere, normal circulating testosterone levels are important for muscle function, erythropoiesis and bone mineralization. Since these issues are commonly affected in the elderly for various reasons, hypotestosteronemia, whenever occurs, can play an additive negative role and weaken patients' quality of life. In addition testosterone has been recently involved in the pathogenesis of metabolic syndrome, a cohort of abnormalities strictly linked to cardiovascular diseases [23]. Therapy with androgens in elderly is indicated only in symptomatic hypogonadal patients without evidence of absolute (prostate cancer, breast cancer) contraindications and thorough examination of prostate-specific antigen, red blood cell count, hematocrit and lipid profile. Transdermal preparations (gel) are currently advised in order to prevent supraphysi-

ological peaks following parenteral administration but are expensive. Our few patients who underwent parenteral testosterone therapy reached satisfactory circulating levels, suffered neither significant side-effects nor biochemical drawbacks, and showed improvement in sexual activity and well-being.

Finally, most studies have found an increased mortality due to cardiovascular and cerebrovascular diseases in HYPO, mainly in women [1, 3, 24-26]. The possibility that sex steroids and glucocorticoid replacement therapy, may increase vascular risks is under discussion and underlines the need to avoid over-replacement [1, 3, 11].

Since GH deficiency and its related adverse metabolic profile (visceral obesity, impaired glucose tolerance, insulin resistance, and dyslipidemia) can contribute to the excess of cardiovascular mortality and worsen osteoporosis and protein catabolism. GH replacement therapy has been advocated in adult subjects after careful evaluation and exclusion of contraindications (malignancy and proliferative diabetic retinopathy) [27]. In the elderly, this therapy should be proposed with special caution, with a mean dose lower than in younger patients, i.e. a 0.1-0.3 mg/day regimen, and scheduled control of metabolic parameters and IGF-I [26, 27]. In our small series, only 3 patients started rhGH replacement therapy (mean maintenance dose 0.3 mg/day s.c.); all patients experienced an improvement in quality of life (assessed by QoL questionnaire score) over the time and none reported side-effects.

In sum, HYPO is an often neglected and subtle condition, which in the elderly is frequently under-diagnosed because it is not investigated. Many correlated symptoms overlap with those that are characteristic of the aging process. The delayed diagnosis and therapy of HYPO can lead to serious systemic complications. The prevalent etiology of HYPO (i.e. pituitary tumors) can now be quite satisfactorily managed, also in the elderly, by means of combined approaches. Greater awareness of this disease in the old population and of its heterogeneous clinical and biochemical features would allow earlier diagnosis and treatment, resulting in a significant improvement in the quality of life of these patients.

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