crinologist to make the correct diagnosis. More recently clinical geneticist are helping to make the genetic diagnosis and therefore sometimes changing the nature of a planned operation and helping families to prevent major morbidities. Characterisation by a pathologist is crucial as treatment options are also widening and special assessment such as immunostaining for somatostatin receptors or MGMT. Special imaging with metomidate PET-CT could lead to the right choice of next step. The role of radiotherapist and oncologist intervening in the severe cases can be life-prolonging for many patients. Importantly the endocrinologist is keeping this orchestra of specialist together and guides the patient management and long-term follow-up.

KEYWORDS: pituitary tumours, treatment options, patient management.

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TREATMENT OF GH DEFICIENCY IN ADULTS GROWTH HORMONE IS THE MOST FREQUENT PITUITARY HORMONE DEFICIT AND IS AFFECTED FIRST

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Hypopituitarism results from complete or partial deficiency of pituitary hormones and is caused by a variety of structural lesions or trauma involving the hypothalamus or pituitary gland (most often pituitary adenomas). There is a varying sensitivity of the different anterior pituitary hormones to pathological damage. The usual sequential pattern of hormonal deficiencies is the loss of growth hormone (GH) followed by gonadotropins, TSH and ACTH. The reason why GH is the most frequent pituitary hormone deficit and affected first is not known. GH axis is most vulnerable to cranial irradiation. Patients who received cranial irradiation frequently develop isolated GH deficiency. GH deficiency is more common as part of multiple pituitary hormone deficiency. Hypopituitary patients have increased sick days, lower health status and those with GH deficiency have less working capacity. Furthermore, findings of several studies have shown excess mortality in patients with hypopituitarism. Hypopituitarism removes the natural survival advantage that women have over men. Highest mortality is among younger patients, women and patients with diabetes insipidus. A recent study from Sweden shows a decline in mortality in patients optimally replaced including GH replacement therapy.

Diagnosing adults with GH deficiency

Adult GH deficiency is associated with adverse physical, metabolic and quality of life symptoms. Adults with GH deficiency have reduced body lean mass ,excess abdominal fat mass (truncal fat, weight waist circumference), decreased bone mineral density, decreased energy level ,social isolation, inadequate initiative and generally decreased quality of life. The clinical features of GH deficiency are not distinctive and clinical suspicion should be confirmed by GH stimulation tests. A GH stimulation test with abnormally low peak serum GH concentrations and low insulin growth factor-I (IGF-I) concentrations is diagnostic in a patient with high pretest probability of having GH deficiency. Normal IGF-I concentrations do not exclude a diagnosis of GH deficiency in adults. Insulin tolerance test is recommended as the gold standard test. If contraindicated other stimulation tests are suggested. If GH deficiency is isolated then two stimulation tests may be required. Severe GH deficiency can be diagnosed without any testing if the patient has three pituitary deficiencies and low serum IGF-I concentrations. In obesity GH secretion is reduced, GH clearance is enhanced and stimulated GH secretion is reduced thus causing functional hyposomatotropism. This functional hyposomatotropism in obesity is reversed by weight loss. Considering the rising prevalence of obesity, GH stimulation tests should be avoided in obese subjects with very low pretest probability.

GH dosing and patient monitoring

In adults with GH deficiency, the goal of growth hormone replacement is to improve wellbeing, reduce cardiovascular risk, increase bone density and normalize body composition. Recombinant human growth hormone is available for daily subcutaneous injections. Initial low GH doses are preferred and the recommended starting dose is 0.2—0.4 mg/day for patients younger than 60 years and 0.1—0.2 mg /day for patients older than 60 years. For younger transition patients (<30 years) the starting dose is 0.4—0.5 mg/ day. After initiation of GH replacement treatment**,** follow up is usually planned at intervals of 2—3 months, when the dose of GH can be adjusted by increments of 0.1—0.2mg/day based on clinical response, IGF-I and side effects. The GH dose should be titrated towards mid-normal IGF-I concentration adjusted for age. The dose should be reduced if side effects occur such as fluid retention, muscle and joint stiffness and pain, peripheral edema and carpal tunnel. Thyroid and adrenal function need to be assessed before and after starting growth hormone replacement because GH replacement may unmask central hypothyroidism and secondary adrenal insufficiency so the doses of replacement need to be adjusted. Dose adjustments needs to be done in women who are on oral estrogen. Higher GH doses are needed since estrogen attenuates the serum IGF1 response to GH. Once the dose is stabilized, clinicians should monitor for efficacy.

Efficacy of GH replacement therapy in adult GH deficiency

Overall GH replacement results in improvement in body composition and bone mineral density in particular in men and those with low bone mass. Visceral adipose tissue mass decreases by 9% and lean body mass improves up to 7%. Muscle strength improves. Results from a re-

cent study, using accurate assessment of left ventricular (LV) mass by cardiac magnetic resonance, demonstrated reduced cardiac mass in patients with adult onset GH deficiency and increase in cardiac mass after 1 year of GH replacement. Improved quality of life after seven years of GH replacement is reported with most marked improvement in patients with low baseline quality of life. Most of the improvement is seen during the first year of treatment but it improves further with time. All effects of GH replacement therapy are sustained for long period of time (over 10 years). What is helpful in evaluating the success of GH replacement therapy and in the deciding to continue GH replacement therapy? A recent study shows that IGF-I concentrations, quality of life, total cholesterol and waist circumference response to 2 years of GH replacement therapy predict the response.

Safety of GH replacement therapy

Safety concerns with GH replacement therapy are diabetes mellitus, malignancies occurring de novo and re-growth of residual pituitary mass .GH reduces insulin sensitivity and therefore the concern that this therapy might induce diabetes mellitus. Data from two large data bases report a slightly increased prevalence of diabetes mellitus in particular in those who are obese and who have a strong family history of diabetes mellitus while data from the most recent database show that four years of GH replacement therapy did not adversely affect glucose homeostasis in the majority of adults with GH deficiency. Available data do not suggest an increased risk of de novo malignancies or recurrence or re-growth of residual pituitary tumor. **Conclusion.** GH replacement treatment in adult GH deficient patients appears to have favorable long-term efficacy and safety profile.

KEYWORDS: growth hormone, IGF-I, GH replacement therapy.

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CHALLENGES IN PROLACTINOMA MANAGEMENT

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Case1: A woman with a long history of cabergolin treatment

Patient *B.*, 40 years, after a long period (17 years) of cabergoline treatment due to a residual prolactinoma after transnasal adenomectomy (because of bromocriptine intolerance) at 19 years of age. In the ensuing years the patient had 4 spontaneous pregnancies at the age of 27, 28, 31 and 33 years. During gestation period and breastfeeding agonist therapy was discontinued, Cabergoline therapy was discontinued during the intergestational periods due to high levels (30 000—40 000 mu/ml) of prolactin. On her last visit to the endocrinologist normprolactinemia was confirmed (0,25 mg/wk Carbegoline). FSH was on reproductive levels. According to the MRI, a cystic tumor is visualized of endoparacellular localization, sized 13×15×20 mm, with signs of postoperative alterations. Echocardiologic examination was performed, no valve pathology was found.

Case 2. A case of galactorrhea due to self-prescribed estrogene-treatment in a male-to-female transgender

This story began at the early 70's, while in the former USSR no law regulation existed on gender dysphoria and even the mere idea about the existence of such a problem was unfamiliar to Russian physicians. Patient *P.* was a normal full term male baby. At the age of 10, he started feeling a desire to wear girls' clothing. At the age of 15, he came to a firm conclusion that he was a girl, and thus started urinating like one (squatting), wearing lipstick and makeup. He also greatly suffered from having a «deformity» — his male reproductive organs. At the age of 17, working as a hospital cleaner, he began injecting himself with estrogenes and progesterone which lead to the development of mammary glands and, in the end, constant milk flow from the breasts. To receive a passport he showed this effect to the police staff and officially changed his gender to female. At the age of 23 the mammary gland showed a development stage corresponding to that of a 15—16 year old girl (due to periodical intake of estrogens) with a nipple discharge (sizable droplets upon applying pressure — galactorrhea ++). He insisted on castration and penile amputation due to feelings of shame which came from having a «deformity» inappropriate to his gender. Skull x-ray revealed normal sella turcica in terms of form and size, however there were signs of increased intracranial pressure. The thyroid gland functions were within normal limits. Radioimmunoassay was performed using standard radioimmunoassay kits (Sorin). A slightly elevated prolactin level in the blood was revealed — 24 ng/ml (normal range for males, 4—15 ng/ml). Given multiple suicide attempts, unsuccessful psychiatric treatment, female gender, and a female social role, the patient ultimately underwent castration and feminizing genitoplasty at the age of 27 as a means of social rehabilitation. Some time after surgery, the patient regained interest in life. Surgical and hormonal treatment resulted in the patient exhibiting an overwhelming maternal instinct. Being single, the patient secured her right to adopt a child, simulated pregnancy and was discharged from a maternity hospital with a son. Immediately after «labor», the patient showed significant increase in galactorrhea (+++) and forceful milk ejection reflex. The baby was nursed until the age of 6 months. These findings lead us to believe that galactorrhea in the patient may be due to several factors.

1. Increased prolactin level as a result of estrogen use and treatment with cyproterone acetate. Estrogens have long been known to increase prolactin levels in the blood, and similar properties of cyproterone acetate were shown by *K. Schmidt-Golewizer et al.*

2. Increased intracranial pressure. Its role in disorders of the neuroendocrine system (galactorrhea in particular) was demonstrated by *R. Paterson*.