and PEGV make it attractive to use the two drugs in combination. Maybe it is time to challenge the existing concepts of treatment and monitoring of patients with acromegaly.

KEYWORDS: acromegaly, IGF-I, somatostatin, pegvisomant.

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CUSHING'S SYNDROME: HOW TO SCREEN, DIAGNOSE AND TREAT TODAY WITH LINK TO THE FUTURE

R. Feelders

Erasmus University Medical Center, Rotterdam, Netherlands

Cushing's disease (CD), caused by a corticotroph pituitary adenoma, is associated with multi-system morbidity resulting in an impaired quality of life. When untreated or suboptimally treated, CD can lead to an increased mortality with cardiovascular disease as leading cause of death. Recently an etiological role for somatic mutations in ubiquitin specific peptidase 8 gene (USP8) has been identified in a subset of corticotroph adenomas. Inactivation of USP8 leads to increased epidermal growth factor receptor (EGFR) signaling and subsequently ACTH synthesis. EGFR may become a new therapeutic target in CD. Because of the gradual development of symptoms and the overlap in features of the metabolic syndrome, it can take years before the diagnosis CD is established. First-line screening tests are available to identify patients with CD, i.e. 24 h urinary free cortisol excretion, the overnight 1 mg dexamethasone suppression test and measurement of late night salivary cortisol levels (LNSC). LNSC can also be helpful to differentiate CD from conditions that are accompanied by activation of the pituitary-adrenal axis ('pseudo-Cushing states'), e.g. psychiatric disorders. Rarely, CD has a cyclical pattern which can hamper biochemical diagnosis. Preliminary data show that measurement of cortisol in scalp hair can reveal episodic cortisol overproduction in these patients. Transsphenoidal adenomectomy is the first choice of treatment for CD and remission rates vary between 60 and 90%. Treatment modalities for patients with persistent or recurrent disease include repeat surgery, radiotherapy, medical therapy and bilateral adrenalectomy. Medical therapy for CD can be classified into pituitary-directed drugs, adrenal-blocking drugs and glucocorticoid receptor antagonists. Dopamine and somatostatin receptors have been identified as targets for pituitary-directed drug therapy. The majority of ACTH-secreting pituitary adenomas expresses the dopamine receptor subtype 2 (DA2) and several studies show that the DA2 agonist cabergoline can normalize cortisol production in 25—40% of CD patients. Of the 5 known somatostatin receptor subtypes (sst), corticotroph pituitary adenomas predominantly express sst5, whereas sst2 expression is low due to down-regulating effects of high cortisol levels. Pasireotide is a universal somatostatin analog with high affinity for sst5 and the formulation for subcutaneous administration was recently approved for treatment of CD in Europe and the USA. A study with longacting pasireotide in CD is underway. Combined targeting of DA2 and sst5 with cabergoline and pasireotide showed promising results. Another potential therapeutic target includes cyclin-dependent kinases which were shown to be upregulated in corticotroph adenomas and which can promote cell growth via deregulation of the cell cycle. Metyrapone and ketoconazole are the most widely used adrenal blocking drugs. LCI699 and COR-003 are recently developed inhibitors of steroidogenesis and are currently under investigation in multicenter trials. Mifepristone is the only available glucocorticoid receptor antagonist and was recently approved in the USA for treatment of hyperglycemia related to CD. Importantly, morbidity of CD is not or only partially reversible in a substantial number of patients which is possibly related to the duration of pre-existing hypercortisolism. Therefore, after diagnosis cortisol production should be rapidly normalized with concomitant careful treatment of (cardiovascular) co-morbidity. Long-term follow-up is needed for CD patients to monitor complications of hypercortisolism and to detect recurrent disease.

KEYWORDS: cushing's syndrome, pituitary adenoma, ACTH, cortisol.

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UPDATE ON THE MULTIDISCIPLINARY MANAGEMENT OF PITUITARY TUMOURS

M. Korbonits

Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

The pituitary gland is one of most fascinating organs of the body, as it has centrally important functions and also it is located in a unique anatomical position. It is the leader of the endocrine orchestra regulating multiple functions and it is sitting below the optic crossing and in-between the carotid arteries therefore no surprise that management of diseases of the pituitary requires an orchestra of expert colleagues itself. Starting with the diagnosis, we rely on family doctors, neurologists, rheumatologists, dermatologists, orthopaedic specialist, neurosurgeons, dentists, gynaecologists, cardiologists, ophthalmologists and optometrists but even jewellers (ring enlargements) and to make or at least suggest the diagnosis of acromegaly, Cushing's disease, prolactinoma, TSHoma, diabetes insipidus etc. While the diagnosis often is simple, in other cases numerous tests and discussions are needed to come to the right conclusions: skills of an interventional radiologists doing venous catheterisation or a vigilant biochemist testing for macroprolactin or the hook effect or special tests to solve the thyroid hormone resistance-TSHoma dilemma, helps out the endo-

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

V. Popovic[1,2]

[1]Belgrade University School of Medicine, Belgrade, Serbia;
[2]University Clinical Center, Belgrade, Serbia

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-