ΔΙΑΤΑΡΑΧΕΣ ΟΠΙΣΘΙΟΥ ΛΟΒΟΥ

Abnormal plasma sodium concentrations in patients treated with desmopressin for cranial diabetes insipidus: results of a long-term retrospective study

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Abstract

Context and objective: Patients with cranial diabetes insipidus (CDI) are at risk of developing both hypernatraemia and hyponatraemia, due to the condition itself or secondary to treatment with vasopressin-analogues or during administration of i.v. fluids. We aimed to assess the frequency and impact of dysnatraemias in the inpatient (INPT) and outpatient (OPT) setting in desmopressin-treated CDI, comparing those with normal thirst with those with abnormal thirst.
Design: The study included 192 patients with cranial diabetes, who were identified from the Beaumont Pituitary Database, a tertiary referral centre. Retrospective case note audit was performed and the clinical and biochemical information of 147 patients with CDI were available for analysis.
Results: A total of 4142 plasma sodium measurements for 137 patients with normal thirst, and 385 plasma sodium measurements for ten patients with abnormal thirst were analysed. In those with normal thirst, the most common OPT abnormality was mild hyponatraemia (pNa^+ 131–134 mmol/l) in 27%, while 14.6% had more significant hyponatraemia ($pNa^+ \leq 130$ mmol/l). Of those patients with normal thirst, 5.8% were admitted due to complications directly related to hyponatraemia. Compared with patients with normal thirst, those with abnormal thirst were more likely to develop significant OPT hypernatraemia (20% vs 1.4%, $P=0.02$) and significant INPT hyponatraemia (50% vs 11.1%, P 0.02).
Conclusion: OPT management of CDI is complicated by a significant incidence of hyponatraemia. In contrast, OPT hypernatraemia is almost exclusively a complication seen in adipsic CDI, who also had more frequent INPT hyponatraemia. CDI associated with thirst disorder requires increased physician attention and patient awareness of potential complications.

European Journal of Endocrinology (2015) **172**, 243–250

Diagnostic Accuracy of Copeptin in the Differential Diagnosis of the Polyuria-polydipsia Syndrome: A Prospective Multicenter Study Katharina Timper et al, *Journal of Clinical Endocrinology and Metabolism 100(6), pp. 2268–2274*

Context: The polyuria-polydipsia syndrome comprises primary polydipsia (PP) and central and nephrogenic diabetes insipidus (DI). Correctly discriminating these entities is mandatory, given that inadequate treatment causes serious complications. The diagnostic "gold standard" is the water deprivation test with assessment of arginine vasopressin (AVP) activity. However, test interpretation and AVP measurement are challenging. Objective: The objective was to evaluate the accuracy of copeptin, a stable peptide stoichiometrically cosecreted with AVP, in the differential diagnosis of polyuria-polydipsia syndrome. Design, Setting, and Patients: This was a prospective multicenter observational cohort study from four Swiss or German tertiary referral centers of adults >18 years old with the history of polyuria and polydipsia. Measurements: A standardized combined water deprivation/3% saline infusion test was performed and terminated when serum sodium exceeded 147 mmol/L. Circulating copeptin and AVP levels were measured regularly throughout the test. Final diagnosis was based on the water deprivation/saline infusion test results, clinical information, and the treatment response. Results: Fifty-five patients were enrolled (11 with complete central DI, 16 with partial central DI, 18 with PP, and 10 with nephrogenic DI). Without prior thirsting, a single baseline copeptin level >21.4 pmol/L differentiated nephrogenic DI from other etiologies with a 100% sensitivity and specificity, rendering a water deprivation testing unnecessary in such cases. A stimulated copeptin >4.9 pmol/L (at sodium levels >147 mmol/L) differentiated between patients with PP and patients with partial central DI with a 94.0% specificity and a 94.4% sensitivity. A stimulated AVP >1.8 pg/mL differentiated between the same categories with a 93.0% specificity and a 83.0% sensitivity. Limitation: This study was limited by incorporation bias from including AVP levels as a diagnostic criterion. Conclusion: Copeptin is a promising new tool in the differential diagnosis of the polyuria-polydipsia syndrome, and a valid surrogate marker for AVP.

Postoperative Copeptin Concentration Predicts Diabetes Insipidus After Pituitary Surgery Bettina Winzeler et al., *Journal of Clinical Endocrinology and Metabolism 100(6), pp. 2275–2282*

Context: Copeptin is a stable surrogate marker of vasopressin release; the peptides are stoichiometrically secreted from the neurohypophysis due to elevated plasma osmolality or nonosmotic stress. We hypothesized that following stress from pituitary surgery, patients with neurohypophyseal damage and eventual diabetes insipidus (DI) would not exhibit the expected pronounced copeptin elevation. Objective: The objective was to evaluate copeptin's accuracy to predict DI following pituitary surgery. Design: This was a prospective multicenter observational cohort study. Setting: Three Swiss or Canadian referral centers were used. Patients: Consecutive pituitary surgery patients were included. Measurements: Copeptin was measured postoperatively daily until discharge. Logistic regression models and

diagnostic performance measures were calculated to assess relationships of postoperative copeptin levels and DI. Results: Of 205 patients, 50 (24.4%) developed postoperative DI. Post-surgically, median [25th-75th percentile] copeptin levels were significantly lower in patients developing DI vs those not showing this complication: 2.9 [1.9–7.9] pmol/L vs 10.8 [5.2–30.4] pmol/L; $P < .001$. Logistic regression analysis revealed strong association between postoperative copeptin concentrations and DI even after considering known predisposing factors for DI: adjusted odds ratio (95% confidence interval) 1.41 (1.16–1.73). DI was seen in 22/27 patients with copeptin <2.5 pmol/L (positive predictive value, 81%; specificity, 97%), but only 1/40 with copeptin >30 pmol/L (negative predictive value, 95%; sensitivity, 94%) on postoperative day 1. Limitations: Lack of standardized DI diagnostic criteria; postoperative blood samples for copeptin obtained during everyday care vs at fixed time points. Conclusions: In patients undergoing pituitary procedures, low copeptin levels despite surgical stress reflect postoperative DI, whereas high levels virtually exclude it. Copeptin therefore may become a novel tool for early goal-directed management of postoperative DI.

ΜΕΓΑΛΑΚΡΙΑ

Clinical Study | C Schöfl and others | Reasons for uncontrolled acromegaly | 172:4 | 351–356

Failure to achieve disease control in acromegaly: cause analysis by a registry-based survey

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Abstract

Context: Disease control is a prime target in acromegaly treatment. This should be achievable in the vast majority of patients by available treatment options. For unknown reasons, however, a significant number of patients do not achieve disease control.
Objective: To investigate reasons for failure to achieve disease control in long-standing acromegaly.
Design and methods: Survey based on the German Acromegaly Registry database (1755 patients in 57 centres). Questionnaires were sent to 47 centres treating 178 patients with elevated disease markers (IGF1 and GH) at the last documented database visit out of 1528 patients with a diagnosis dated back ≥2 years. Thirty-three centres returned anonymised information for 120 patients (recall rate 67.4%).
Results: Median age of the 120 patients (58 females) was 57 years (range 17–84). Ninety-four patients had at least one operation, 29 had received radiotherapy and 71 had been previously treated medically. Comorbidities were reported in 67 patients. In 61 patients, disease activity had been controlled since the last documented database visit, while 59 patients still had biochemically active disease. Reasons were patients' denial to escalate therapy (23.3%), non-compliance (20.6%), fluctuating insulin-like growth factor 1 (IGF-1) and growth hormone (GH) levels with normal values at previous visits (23.3%) and modifications in pharmacotherapy (15.1%). Therapy resistance (9.6%), drug side effects (4.1%) and economic considerations (4.1%) were rare reasons.
Conclusions: Main reasons for long-standing active acromegaly were patients' lack of motivation to agree to therapeutic recommendations and non-compliance with medical therapy. Development of patient education programmes could improve long-term control and thus prognosis of acromegalic patients.

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The Incidence of Cancer Among Acromegaly Patients: Results From the German Acromegaly Registry David Petroff, et al, *Journal of Clinical Endocrinology and Metabolism 100(10), pp. 3894–3902*

Context: Acromegaly is a rare disease characterized by high serum levels of GH and IGF-1. Animal studies have demonstrated links between these hormones and cancer, but data regarding cancer incidence among acromegaly patients are inconsistent. Moreover, therapy options have changed considerably since many of the aforementioned data were collected. Objective: The objective was to determine whether the overall and site-specific incidence of cancer is comparable to that of the general population. Design and Setting: Data from the German Acromegaly Registry for 446 patients (6656 person-years from diagnosis) treated in seven specialized endocrine centers were analyzed. Main Outcome Measure: Standard incidence ratios (SIRs) were calculated as compared to the general population. Results:

Overall cancer incidence was slightly but not significantly lower than in the general population (SIR, 0.75; 95% confidence interval, 0.55 to 1.00; P = .051) and was not significantly higher for colorectal, breast, thyroid, prostate, and lung cancers. The SIRs of those with GH in the ranges <1, 1–2.5, and ≥2.5 ng/mL were 0.75, 0.44, and 0.92, respectively (P = .94). There was not a significant dependence on normal vs elevated IGF-1 (P = .87), radiation therapy (P = .45), disease duration (P = .96), age at diagnosis (P = .15), or during a period of high GH and IGF-1 from 8 years before to 2 years after diagnosis of acromegaly (P = .41). Conclusions: Cancer screening strategies need to take incidence into account, which does not seem to be substantially higher in treated acromegaly patients than in the general population for any site of cancer.

A giant? Think of genetics: growth hormone-producing adenomas in the young are almost always the result of genetic defects Constantine A. Stratakis
Endocrine 50:272–275 (editorial)

GH treatment

Clinical Study
Open Access

O Cohen-Barak and others | Safety and pharmacokinetics of TV-1106 | 173:5 | 541–551

Safety, pharmacokinetic and pharmacodynamic properties of TV-1106, a long-acting GH treatment for GH deficiency

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Abstract

Background: TV-1106 (Teva Pharmaceuticals) is a genetically fused recombinant protein of human GH (hGH) and human serum albumin, in development for treatment of GH deficiency (GHD). TV-1106 is expected to have an extended duration of action compared to daily GH treatment and may enable a reduction in the frequency of injections and improve compliance and quality of life for adults and children requiring GHD therapy.
Objective: To assess the safety, local tolerability, pharmacokinetics and pharmacodynamics of TV-1106 following single s.c. injections in healthy male volunteers.
Methods: Subjects ($n=56$) were assigned to one of seven ascending dose groups (3–100 mg) and received either a single dose of TV-1106 ($n=6$) or placebo ($n=2$) by s.c. injection.
Results: Eighteen subjects reported 43 adverse effects (AEs), which were mild to moderate; no serious AEs (SAEs) occurred. In 50, 70 and 100 mg groups there were mild to moderate increases in heart rate and systolic blood pressure that significantly correlated with higher levels of IGF1. TV-1106 showed pharmacokinetic characteristics of a long-acting hGH as demonstrated by a terminal elimination half-life of 23–35 h, delayed time of peak concentration, and systemic levels seen up to 7 days after dosing. IGF1 levels increased in a dose-dependent manner, before reaching a plateau, with levels above baseline extending beyond 7 days post dose.
Conclusion: Single administration of TV-1106 up to 100 mg was safe in healthy volunteers. Pharmacokinetics and pharmacodynamics support once-weekly administration in patients with GHD.

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Tumor Recurrence or Regrowth in Adults With Nonfunctioning Pituitary Adenomas Using GH Replacement Therapy N. C. van Varsseveld, et al, *Journal of Clinical Endocrinology and Metabolism 100(8), pp. 3132–3139*

Context: GH replacement therapy (GH-RT) is a widely accepted treatment in GH-deficient adults with nonfunctioning pituitary adenoma (NFPAs). However, some concerns have been raised about the safety of GH-RT because of its potentially stimulating effect on tumor growth. Objective: The aim of this study was to evaluate tumor progression in NFPA patients using GH-RT. Design, Setting, and Patients: From the Dutch National Registry of Growth Hormone Treatment in Adults, a nationwide surveillance study in severely GH-deficient adults (1998–2009), all NFPA patients with ≥ 30 days of GH-RT were selected (n = 783). Data were retrospectively collected from the start of GH-RT in adulthood (baseline). Main Outcome Measure: Tumor progression, including tumor recurrence after complete remission at baseline and regrowth of residual tumor. Results: Tumor progression developed in 12.1% of the patients after a median (range) time of 2.2 (0.1–14.9) years. Prior

radiotherapy decreased tumor progression risk compared to no radiotherapy (hazard ratio = 0.16; 95% confidence interval, 0.09–0.26). Analysis in 577 patients with available baseline imaging data showed that residual tumor at baseline increased tumor progression risk compared to no residual tumor (hazard ratio = 4.5; 95% confidence interval, 2.4–8.2). Conclusions: The findings in this large study were in line with those reported in literature and provide further evidence that GH-RT does not appear to increase tumor progression risk in NFPA patients. Although only long-term randomized controlled trials will be able to draw firm conclusions, our data support the current view that GH-RT is safe in NFPA patients.

Relationship Between Serum IGF-1 and Skeletal Muscle IGF-1 mRNA Expression to Phosphocreatine Recovery After Exercise in Obese Men With Reduced GH Sulaiman R. Hamarneh, et al., *Journal of Clinical Endocrinology and Metabolism 100(2), pp. 617–625*

Context: GH and IGF-1 are believed to be physiological regulators of skeletal muscle mitochondria. Objective: The objective of this study was to examine the relationship between GH/IGF-1 and skeletal muscle mitochondria in obese subjects with reduced GH secretion in more detail. Design: Fifteen abdominally obese men with reduced GH secretion were treated for 12 weeks with recombinant human GH. Subjects underwent 31P-magnetic resonance spectroscopy to assess phosphocreatine (PCr) recovery as an in vivo measure of skeletal muscle mitochondrial function and percutaneous muscle biopsies to assess mRNA expression of IGF-1 and mitochondrial-related genes at baseline and 12 weeks. Results: At baseline, skeletal muscle IGF-1 mRNA expression was significantly associated with PCr recovery ($r = 0.79$; $P = .01$) and nuclear respiratory factor-1 ($r = 0.87$; $P = .001$), mitochondrial transcription factor A ($r = 0.86$; $P = .001$), peroxisome proliferator-activated receptor (PPAR)γ ($r = 0.72$; $P = .02$), and PPARα ($r = 0.75$; $P = .01$) mRNA expression, and trended to an association with PPARγ coactivator 1-α ($r = 0.59$; $P = .07$) mRNA expression. However, serum IGF-1 concentration was not associated with PCr recovery or any mitochondrial gene expression (all $P > .10$). Administration of recombinant human GH increased both serum IGF-1 (change, 218 ± 29 μg/L; $P < .0001$) and IGF-1 mRNA in muscle (fold change, 2.1 ± 0.3; $P = .002$). Increases in serum IGF-1 were associated with improvements in total body fat ($r = −0.53$; $P = .04$), trunk fat ($r = −0.55$; $P = .03$), and lean mass ($r = 0.58$; $P = .02$), but not with PCr recovery ($P > .10$). Conversely, increase in muscle IGF-1 mRNA was associated with improvements in PCr recovery ($r = 0.74$; $P = .02$), but not with body composition parameters ($P > .10$). Conclusion: These data demonstrate a novel association of skeletal muscle mitochondria with muscle IGF-1 mRNA expression, but independent of serum IGF-1 concentrations

Cushing's

Clinical Study | K Ritzel and others | ACTH rise and Cushing's syndrome | 173:2 | 197–204

ACTH after 15 min distinguishes between Cushing's disease and ectopic Cushing's syndrome: a proposal for a short and simple CRH test

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Abstract

Objective: The aim of the present study was to validate criteria of corticotropin-releasing hormone (CRH) stimulation and 8 mg dexamethasone suppression (high-dose dexamethasone suppression, HDDS) to distinguish the etiology of ACTH-dependent Cushing's syndrome.
Subjects and methods: We retrospectively analyzed cortisol and ACTH after the injection of 100 μg human CRH in confirmed Cushing's disease (CD, $n=78$) and confirmed ectopic Cushing's syndrome (ECS, $n=18$). Cortisol and ACTH increase (in percentage above basal ($\%_B$)) at each time point, maximal increase (Δmax $\%_B$), and area under the curve (AUC $\%_B$) were analyzed using receiver operator characteristics (ROC) curve analyses. Cortisol suppression ($\%_B$) after 8 mg of dexamethasone was evaluated as a supplementary criterion.
Results: An increase in ACTH of $\geq 43\%_B$ at 15 min after CRH was the strongest predictor of CD, with a positive likelihood ratio of 14.0, a sensitivity of 83%, a specificity of 94%, a positive predictive value of 98% and a negative predictive value of 58%. All of the other criteria of stimulated ACTH and cortisol levels were not superior in predicting CD in response to CRH injection. The addition of cortisol suppression by dexamethasone did not increase the discriminatory power. However, the combination of a positive ACTH response at 15 min and a positive HDDS test excluded ECS in all cases.
Conclusion: The present findings support the use of plasma ACTH levels 15 min after the injection of human CRH as a response criterion for distinguishing between CD and ECS. The addition of the HDDS test is helpful for excluding ECS when both tests are positive.

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Postoperative follow-up of Cushing's disease using cortisol, desmopressin and coupled dexamethasone-desmopressin tests: a head-to-head comparison *Clinical Endocrinology Volume 83, Issue 2, August 2015, Pages 216–222*

Objective: Predicting the outcome of patients operated on for Cushing's disease (CD) is a challenging task. Our objective was to assess the accuracy of immediate postsurgical plasma cortisol, desmopressin test and the coupled dexamethasone-desmopressin test (CDDT) as predictors of outcome.**Design and patients:** Sixty-seven patients with initial remission and a minimal postsurgical follow-up greater than 18 months were included in this retrospective bicentre study.**Measurements:** Follow-up included 3–6 months followed by yearly 24-h urinary-free cortisol, ACTH and cortisol plasmatic levels, a 1-mg overnight dexamethasone suppression test (1-mg DST), desmopressin test and the CDDT. ROC curves were performed to define the optimal threshold of immediate postsurgical cortisol level and 3- to 6-month desmopressin test and CDDT, as predictors of final outcome in comparison with classical biological markers of recurrence. **Results:** Eleven patients presented recurrence. The patient's median follow-up was 52 months (range, 18–180). As early predictors of

outcome, immediate postsurgical plasma cortisol level <35 nmol/l predicted the lack of recurrence with 93% negative predictive value (NPV), whereas predictive positive value (PPV) was 25%. During the follow-up, the CDDT was more precise than the desmopressin test in predicting the lack of recurrence (100% NPV) when performed in the first 3 years after surgery. Positivity of the CDDT was defined based on ROC curves by ACTH and cortisol increments >50%. The CDDT was highly reproducible, as the same response was observed every year in 91% of the patients. **Conclusions:** Adding the CDDT the first 3 years after surgery to immediate postsurgical cortisol evaluation should allow obtaining an optimal follow-up management of patients operated for Cushing's disease.

Accuracy of repeated measurements of late-night salivary cortisol to screen for early-stage recurrence of Cushing's disease following pituitary surgery Marie Danet-Lamasou, et al., *Clinical Endocrinology Volume 82, Issue 2, August 2015, Pages 260–266*

Objective: The performance of late-night salivary cortisol (LNSC) to accurately screen for postoperative recurrence of Cushing's disease (CD) at an early stage is unknown. The aim of this study was to compare the accuracy of multiple sampling strategies to suggest the optimal number of LNSC samples needed for diagnosing post-surgical recurrences of CD at an early stage. **Design:** Retrospective analysis in a single centre. **Patients and measurements:** Thirty-six patients in surgical remission of CD had successive measurements of LNSC, defined as 'sequences', using a locally modified RIA assay as part of long-term follow-up (69·2 ± 10·6 months). Patients underwent an extensive biochemical evaluation within 3 months before or after a sequence of saliva sampling and were classified as being in remission or in early-stage recurrence. The accuracy of three diagnostic strategies combining two, three or four LNSC results from a sequence was estimated using areas under the ROC curves (AUC), sensitivity, specificity and predictive values. **Results:** Forty-four sequences of LNSC measurements were available. Fifty-two percent of sequences were performed during early-stage recurrence. The intrasequence variability of LNSC was higher during recurrence than during remission (medians of SDs: 2·1 *vs* 0·5 nm; $P < 0·0001$). AUCs from ROC curves ranged from 0·93 to 0·96 depending on the strategy. For 90% sensitivities, the best specificities (92·9% and 90·9%) were achieved by strategies taking into account three or four measurements summarized either by their mean or their maximum value. **Conclusions:** Increase in LNSC concentration is an early abnormality during post-surgical recurrence of CD. However, due to a major within-patient variability of LNSC from 1 day to another, a screening strategy using three or four samples collected on successive days may be recommended to detect early-stage recurrence of CD with a high accuracy.

Accuracy of Late-Night Salivary Cortisol in Evaluating Postoperative Remission and Recurrence in Cushing's Disease Fatemeh G. Amlashi, et al *Journal of Clinical Endocrinology and Metabolism 100(10), pp. 3770–3777*

Context: Late-night salivary cortisol (LNSC) is well-validated in the diagnosis of Cushing's disease (CD). The accuracy of LNSC during follow-up of patients undergoing transsphenoidal surgery (TSS) has not been fully characterized. Objectives: We examined the accuracy of LNSC in establishing remission and identifying recurrence in postoperative patients with CD. Design: This is a retrospective study. Patients: Records of patients with CD who underwent TSS by a single neurosurgeon in our tertiary center (2005–2014) were analyzed (N = 224). Patients were selected for further investigation (n = 165) if there was at least one available LNSC test obtained after TSS (either within 3 months or during long-term follow-up). Extracted data included demographic and clinical characteristics, magnetic resonance imaging and laboratory data (morning serum cortisol, 24-hour urine free cortisol [UFC],

LNSC) . Main Outcomes and Measures: Remission was defined as nadir morning serum cortisol less than 5 mcg/dl and nadir 24-hour UFC less than 23 mcg. Recurrence was considered definite if confirmed surgically or prompted radiotherapy. Results: Surgical remission occurred in 89% of 89 patients with available LNSC data. LNSC, obtained within 3 months of TSS, established remission with 94% sensitivity and 80% specificity at a cutpoint of 1.9 nmol/l (area under the curve [AUC] = 0.90). At a median follow-up of 53.5 months, LNSC established recurrence (75% sensitivity and 95% specificity) at a cutpoint of 7.4 nmol/l (AUC = 0.87), and 24-hour UFC established recurrence (68% sensitivity and 100% specificity) at a cutpoint of 1.6-fold above normal (AUC = 0.82). Conclusions: LNSC may accurately establish remission after TSS and identify recurrence more accurately than 24-hour UFC during long-term follow-up.

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline
Lynnette K. Nieman et al *Journal of Clinical Endocrinology and Metabolism 100(8), pp. 2807–2831*

Objective: The objective is to formulate clinical practice guidelines for treating Cushing's syndrome. Participants: Participants include an Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer. The European Society for Endocrinology co-sponsored the guideline. Evidence: The Task Force used the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews and used the best available evidence from other published systematic reviews and individual studies. Consensus Process: The Task Force achieved consensus through one group meeting, several conference calls, and numerous e-mail communications. Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines. Conclusions: Treatment of Cushing's syndrome is essential to reduce mortality and associated comorbidities. Effective treatment includes the normalization of cortisol levels or action. It also includes the normalization of comorbidities via directly treating the cause of Cushing's syndrome and by adjunctive treatments (eg, antihypertensives). Surgical resection of the causal lesion(s) is generally the first-line approach. The choice of second-line treatments, including medication, bilateral adrenalectomy, and radiation therapy (for corticotrope tumors), must be individualized to each patient.

ΜΗ ΛΕΙΤΟΥΡΓΙΚΑ ΑΔΕΝΩΜΑΤΑ ΥΠΟΦΥΣΗΣ

Clinical Study | G Minniti and others | FSRT for large invasive NFPAs | 172:4 | 433–441

Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response

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Abstract

Objective: We describe the use of fractionated stereotactic radiotherapy (FSRT) for the treatment of large, invasive, nonfunctioning pituitary adenomas (NFPAs). FSRT is frequently employed for the treatment of residual or recurrent pituitary adenomas.

Patients and methods: Sixty-eight patients with a large residual or recurrent NFPAs were treated between April 2004 and December 2012, including 39 males and 29 females (median age 51 years). Visual defects were present in 34 patients, consisting of visual field defects ($n=31$) and/or reduced visual acuity ($n=12$). Forty-five patients had evidence of partial or total hypopituitarism before FSRT. For most of the patients, the treatment was delivered through 5–10 noncoplanar conformal fixed fields using a 6-MV linear accelerator to a dose of 45 Gy in 25 fractions.

Results: At a median follow-up of 75 months (range 12–120 months), the 5- and 10-year actuarial local control were 97 and 91%, respectively, and overall survival 97 and 93%, respectively. Forty-nine patients had a tumor reduction, 16 remained stable, and three progressed. The relative tumor volume reduction measured using three-dimensional (3D) magnetic resonance imaging (MRI) was 47%. The treatment was well tolerated with minimal acute toxicity. Eighteen patients developed partial or complete hypopituitarism. The actuarial incidence of new anterior pituitary deficits was 40% at 5 years and 72% at 10 years. No other radiation-induced complications occurred.

Conclusions: Our results suggest that FSRT is an effective treatment for large or giant pituitary adenomas with low toxicity.

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Dopamine receptor subtype 2 expression profile in nonfunctioning pituitary adenomas and *in vivo* response to cabergoline therapy Leonardo Vieira Neto, et al *Clinical Endocrinology Volume 83, Issue 2, Pages 739–746,*

Objectives: To determine the dopamine receptor subtype 2 (DR2) mRNA levels and protein expression and to evaluate the effect of adjuvant cabergoline therapy on tumour volume (TV) in patients with postoperative residual nonfunctioning pituitary adenoma (NFPA). **Methods:** The mRNA expression was quantified by real-time RT-PCR (TaqMan®), and protein expression was evaluated by immunohistochemistry. Tumours were classified according to the percentage of immunostained cells for DR2 as scores 1 (<50% of stained cells) or 2 (≥50%). Cabergoline was started at least 6 months after surgery in nine patients with residual tumours (3 mg/week). The cabergoline effect was prospectively evaluated by magnetic resonance imaging using three-dimensional volume calculation. TV reduction >25% was considered significant. **Results:** The DR2 mRNA expression was variable but was

observed in 100% of the samples (*N* = 20). DR2 protein expression was also observed in all the tumours (*N* = 34). Twenty-nine tumours (85%) were classified as score 2. The median DR2 mRNA expression was higher in the tumours classified as score 2 compared with score 1 (*P* = 0·007). TV reduction with cabergoline therapy was observed in 67% of the patients (6/9). The median TV before and after 6 months of treatment was 1·90 cm^3 (0·61–8·74) and 1·69 cm^3 (0·36–4·20) [*P* = 0·02], respectively. **Conclusion:** In conclusion, DR2 is expressed in all adenomas and the majority of the patients in this study displayed tumour shrinkage on cabergoline (CAB) therapy. Thus, CAB might be useful in adjuvant therapy in NFPA patients with residual tumours after surgery

Clinical outcomes in patients with nonfunctioning pituitary adenomas managed conservatively Amir H. Sam, et al *Clinical Endocrinology Volume 83, Issue 6, December 2015, Pages 861–865*

Context: The natural history and the optimum management of patients with nonfunctioning pituitary adenomas (NFPAs) are unclear. **Objective:** Our objective was to characterize the natural history of patients with NFPAs managed conservatively. **Design and patients:** We conducted a retrospective analysis of patients presenting to a tertiary referral centre between 1986 and 2009. Patients with pituitary adenomas and no clinical or biochemical evidence of hormonal hypersecretion were included. Those presenting with apoplexy or a radiological follow-up period of less than 1 year were excluded. The pituitary imaging for all patients was re-examined by two neuroradiologists in consensus. **Outcome measures:** The outcome measures were change in tumour size and pituitary hormone function. **Results:** Sixty-six patients were managed conservatively for a mean follow-up period of 4·3 years (range: 1–14·7). Forty-seven (71%) had a macroadenoma, and nineteen (29%) had a microadenoma. Tumour size decreased or remained stable in 40% of macroadenomas and 47% of microadenomas. The median annual growth rate of enlarging macroadenomas and microadenomas was 1·0 mm/year and 0·4 mm/year, respectively. The median annual growth rate of macroadenomas was significantly higher than that of microadenomas (*P* < 0·01). Sixty-eight percentage of patients with a macroadenoma had pituitary hormone deficiency in one or more axes, compared to 42% of those with a microadenoma. **Conclusion:** Patients with NFPAs without optic chiasm compression can be managed conservatively. All patients need pituitary function assessment, irrespective of tumour size. These findings provide clinically relevant data for the management of patients with NFPAs.

Excess Mortality in Women and Young Adults With Nonfunctioning Pituitary Adenoma: A Swedish Nationwide Study Daniel S. Olsson et al*. Journal of Clinical Endocrinology and Metabolism 100(7), pp. 2651–2658*

Context: Patients with hypopituitarism of various etiologies have excess mortality. The mortality in patients with nonfunctioning pituitary adenoma (NFPA), regardless of pituitary function, is less well studied. Objective: Our aim was to investigate mortality in patients with NFPA and to examine whether age at diagnosis, gender, tumor treatments, or hormonal deficiencies influence the outcome. Design: NFPA patients were identified and followed up in nationwide health registries in Sweden, 1987–2011. The criteria for identification were tested and validated in a subpopulation of the patients. Settings: This was a nationwide, population-based study. Patients: A total of 2795 unique patients with NFPA (1502 men, 1293 women) were identified and included in the study. Mean age at diagnosis was 58 years (men, 60 y; women, 56 y) and mean follow-up time was 7 years (range 0–25 y).

Intervention: There were no interventions. Main Outcome Measures: Standardized mortality ratios (SMRs) and annual incidence rates were calculated using the Swedish population as reference and presented with 95% confidence intervals.
Results: Annual incidence of NFPA was 20.3 (18.8–21.9) cases per 1 million inhabitants. During the observation period, 473 patients died against an expected 431, resulting in an SMR of 1.10 (1.00–1.20). Patients diagnosed at younger than 40 years of age had an increased SMR of 2.68 (1.23–5.09). The SMR for patients with hypopituitarism (n = 1500) was 1.06 (0.94–1.19), and for patients with diabetes insipidus (n = 145), it was 1.71 (1.07–2.58). The SMR was increased in women with NFPA (1.29; 1.11–1.48) but not in men (1.00; 0.88–1.12). Women, but not men, with a diagnosis of hypopituitarism and/or diabetes insipidus also had an increased mortality ratio. SMRs due to cerebrovascular (1.73; 1.34–2.19) and infectious diseases (2.08; 1.17–3.44) were increased, whereas the SMR for malignant tumors was decreased (0.76; 0.61–0.94). Conclusions: This nationwide study of patients with NFPA showed an overall excess mortality in women and in patients with a young age at diagnosis. Increased mortality was seen for cerebrovascular and infectious diseases.

Cerebrovascular Events, Secondary Intracranial Tumors, and Mortality After Radiotherapy for Nonfunctioning Pituitary Adenomas: A Subanalysis From the Dutch National Registry of Growth Hormone Treatment in Adults N. C. van Varsseveld, et al., *Journal of Clinical Endocrinology and Metabolism 100(3), pp. 1104–1112*

Context: Radiotherapy is frequently administered as adjuvant treatment in patients with clinically nonfunctioning pituitary adenomas (NFPAs). However, concerns have been raised about potential long-term side effects, including cerebrovascular events (CVEs) and secondary intracranial tumors. Objective: The aim of this study was to analyze the risk of CVEs, secondary intracranial tumors, and mortality in irradiated (IRR) NFPA patients, compared with NFPA patients who were not irradiated (non-IRR). Design, Setting, and Patients: The study cohort included 806 patients with a NFPA from the Dutch National Registry of Growth Hormone Treatment in Adults, a nationwide long-term surveillance study in severe GH-deficient adult patients. IRR patients (n = 456) were compared with non-IRR patients (n = 350). Main Outcome Measures: CVEs, secondary intracranial tumors, and mortality were measured. Results: Sixty-nine subjects developed a CVE. In men, but not in women, the incidence of a CVE was significantly higher in IRR patients than in non-IRR patients (hazard ratio 2.99, 95% confidence interval 1.31–6.79). A secondary intracranial tumor developed in five IRR patients and two non-IRR patients. After adjustment for age, radiotherapy was not associated with mortality. Conclusions: The incidence of secondary intracranial tumors and mortality did not differ between IRR and non-IRR patients. However, a CVE was found significantly more frequently in IRR men but not in women. Further research into the long-term effects of cranial radiotherapy seems mandatory. The potential risks of radiotherapy have to be taken into account when radiotherapy is considered in NFPA patients, and long-term follow-up is recommend

ΥΠΟΘΑΛΑΜΟ-ΕΠΙΝΕΦΡΙΔΙΑΚΟΣ ΑΞΟΝΑΣ

The modulation of corticosteroid metabolism by hydrocortisone therapy in patients with hypopituitarism increases tissue glucocorticoid exposure

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Abstract

Context: Patients with hypopituitarism have increased morbidity and mortality. There is ongoing debate about the optimum glucocorticoid (GC) replacement therapy.
Objective: To assess the effect of GC replacement in hypopituitarism on corticosteroid metabolism and its impact on body composition.
Design and patients: We assessed the urinary corticosteroid metabolite profile (using gas chromatography/mass spectrometry) and body composition (clinical parameters and full body DXA) of 53 patients (19 female, median age 46 years) with hypopituitarism (33 ACTH-deficient/20 ACTH-replete) (study A). The corticosteroid metabolite profile of ten patients with ACTH deficiency was then assessed prospectively in a cross over study using three hydrocortisone (HC) dosing regimens (20/10 mg, 10/10 mg and 10/5 mg) (study B) each for 6 weeks. 11 beta-hydroxysteroid dehydrogenase 1 (11β-HSD1) activity was assessed by urinary THF + 5α-THF/THE.
Setting: Endocrine Centres within University Teaching Hospitals in the UK and Ireland.
Main outcome measures: Urinary corticosteroid metabolite profile and body composition assessment.
Results: In study A, when patients were divided into three groups – patients not receiving HC and patients receiving HC $\leq$ 20 mg/day or HC $>$ 20 mg/day – patients in the group receiving the highest daily dose of HC had significantly higher waist-to-hip ratio (WHR) than the ACTH replete group. They also had significantly elevated THF + 5α-THF/THE ($P = 0.0002$) and total cortisol metabolites ($P = 0.015$). In study B, patients on the highest HC dose had significantly elevated total cortisol metabolites and all patients on HC had elevated THF + 5α-THF/THE ratios when compared to controls.
Conclusions: In ACTH-deficient patients daily HC doses of $>$ 20 mg/day have increased WHR, THF + 5α-THF/THE ratios and total cortisol metabolites. GC metabolism and induction of 11β-HSD1 may play a pivitol role in the development of the metabolically adverse hypopituitary phenotype.

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Association of Sleep Duration and Quality With Alterations in the Hypothalamic-Pituitary Adrenocortical Axis: The Multi-Ethnic Study of Atherosclerosis (MESA) Cecilia Castro-Diehl, et al. *Journal of Clinical Endocrinology and Metabolism 100(8), pp. 3149–3158*

Context: Short sleep duration and poor sleep quality are associated with cardiovascular outcomes. One mechanism proposed to explain this association is altered diurnal cortisol secretion. Objective: The objective of the study was to examine the associations of sleep duration and sleep quality with diurnal salivary cortisol levels. Design: This was a cross-sectional analysis using data from examination 5 (2010–2012) of the Multi-Ethnic Study of Atherosclerosis. Actigraphy-based measures of sleep duration and efficiency were collected over 7 days, and salivary cortisol samples were collected over 2 days from participants aged 54–93 years (n = 600 with analyzable data). Results: Shorter average sleep duration (<6 h/night) was associated with less pronounced late decline in cortisol [2.2% difference in slope; 95% confidence interval (CI) 0.8–3.7; P ≤ .01] and less pronounced wake-to-bed slope (2.2% difference; 95% CI 1.0–3.4; P ≤ .001) compared with longer sleep duration (≥6 h/night). Lower sleep efficiency (<85%) was associated with less pronounced early decline in cortisol (29.0% difference in slope; 95% CI 4.1–59.7; P < .05) compared with higher sleep efficiency (≥85%). Subjects reporting insomnia had a flatter cortisol awakening response (−16.1% difference in slope; 95% CI −34.6 to −0.1; P < .05) compared with those not reporting insomnia. Conclusions: Shorter sleep duration, lower sleep efficiency, and insomnia are associated with alterations in diurnal cortisol levels consistent with changes in hypothalamic-pituitary-adrenal regulation.

Abnormal Responsiveness to Dexamethasone-Suppressed CRH Test in Patients With Bilateral Adrenal Incidentalomas D. A. Vassiliadi, et al., *Journal of Clinical Endocrinology and Metabolism 100(9), pp. 3478–3485*

Context: The bilateral formation of nodules indicates that the pathogenesis of bilateral adrenal incidentalomas (AI) may differ from that of unilateral AI. A possible role of hypothalamo-pituitary-adrenal (HPA) axis dysregulation in their formation has not been investigated. Objective: The objective of the study was to evaluate the presence of altered feedback regulation of HPA axis in patients with bilateral AI. Design: The dexamethasone (DEX) suppression-CRH test was used to assess ACTH and cortisol responses in controls and patients with unilateral and bilateral AI. Setting: The study was conducted at endocrine departments of two tertiary centers. Patients: We studied 24 controls and 39 patients with unilateral and 46 with bilateral AI. Interventions: All subjects underwent standard low-dose dexamethasone suppression followed by iv bolus administration of human CRH (100 μg). Results: Bilateral AI had higher levels of ACTH and cortisol after the DEX-CRH challenge compared with both controls (P < .01 for ACTH and P < .001 for cortisol) and unilateral AI (P

< .01 for ACTH and cortisol). A positive response, defined as peak ACTH greater than 10 pg/mL at 15 and/or 30 minutes followed by a significant rise in cortisol levels, was noted in 41.3% of bilateral vs 2.6% in unilateral AI (P < .001). Bilateral responders did not differ from nonresponders in demographic or hormonal characteristics, but they had larger total adrenal size compared with nonresponders. Conclusions: A significant proportion of patients with bilateral AI demonstrate positive responses to the DEX-CRH test compared with unilateral AI, providing ground for potential involvement of HPA axis dysregulation in the pathogenesis, in at least a subgroup, of bilateral AI patients.

ΝΕΥΡΟΕΝΔΟΚΡΙΝΕΙΣ ΟΓΚΟΙ

Comparison of the Utility of Cocaine- and Amphetamine-Regulated Transcript (CART), Chromogranin A, and Chromogranin B in Neuroendocrine Tumor Diagnosis and Assessment of Disease Progression R. Ramachandran*, Journal of Clinical Endocrinology and Metabolism 100(4), pp. 1520–1528*

Context: Prognosis in patients with neuroendocrine tumors (NETs) is often poor, frequently reflecting delayed diagnosis. Hence, accurate and practical NET markers are needed. Cocaine- and amphetamine-regulated transcript (CART) peptide is a potential novel NET marker. Design and Participants: Circulating levels of CART peptide and the established NET markers chromogranin A (CgA) and chromogranin B (CgB) were measured using RIA in 353 patients with NET (normal renal function) and in controls. Clinical data were collected retrospectively. Main Outcome Measure(s): The comparative and combined utility of CART, CgA, and CgB for diagnosis and assessment of disease progression was measured in different NET subtypes. Results: CgA and CgB in combination improved diagnostic accuracy in patients with gut NETs, nongastroenteropancreatic NETs, and NETs with an unknown primary origin compared with each biomarker alone. Measuring CART did not further improve diagnosis in these NET subtypes. For pancreatic NETs, CgB was superior to CgA and CART in detecting stable disease ($P < .007$), whereas CgA and CART in combination were most effective in identifying progressive disease. In phaeochromocytomas/paragangliomas (PCC/PGL), CART was the most useful biomarker for identifying stable ($P < .001$) and progressive ($P = .001$) disease. Consistent with this, plasma CART decreased following PCC/PGL tumor resection, remaining low in all patients in remission, but increasing in those with progressive disease. Conclusions: CART is a useful marker for identifying progressive pancreatic NETs. CART is superior to CgA and CgB in detecting stable and progressive PCC/PGLs, and may have a role as a surveillance marker for PCC/PGL patients.