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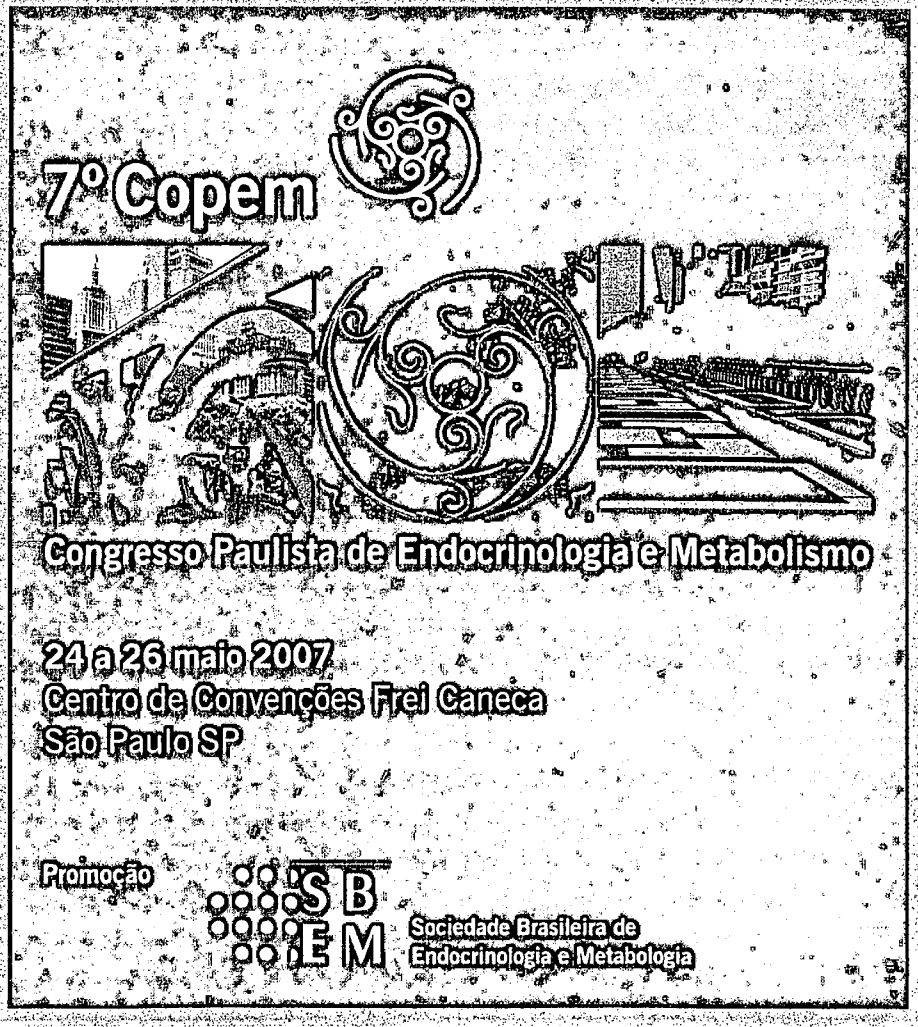

06.008

GROWTH HORMONE (GH) RESPONSE TO GROWTH HORMONE-RELEASING PEPTIDE-2 IN GH-DEFICIENT LITTLE MOUSE.

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Objective: Investigate a possible direct, growth hormone-releasing hormone (GHRH)-independent action of a growth hormone secretagogue, GHRP-2, on pituitary somatotrophs and assessment of the regulation of plasma ghrelin in the presence of inactive GHRH receptors (GHRH-R). Design: Serum GH responses to acutely injected GHRP-2 in the lit/lit mice, a model of GH deficiency due to a mutated GHRH-R, were compared to those observed in heterozygous (lit/+) littermates as well as wild-type (+/+) C57BL/6J mice. **Methods:** In vitro determinations were carried out by immunoassay: in-house specific RIA for mGH, rat RIA kits for IGF-I and ghrelin and a specifc ELISA kit for mouse leptin. In vivo bioassay was based on a previously described mouse body weight gain assay. **Results:** Unexpectedly, after administration of 10 µg GHRP-2 to lit/lit mice, a GH release of 9.3±1.53 was observed compared to 1.04±1.15 ng/ml for the controls (P<0.001). In comparison, an intermediate GH release of 34.5±9.66 was induced in lit/+ and a high GH response of 125±35.3 ng/ml in wild type mice. After 2 weeks of 10µg GHRP-2/day body weight increased (P=0.02) and serum leptin levels rose (P=0.034). In fasted lit/lit compared to fasted wild type mice, plasma ghrelin levels were significantly lower while in the fed state unexpectedly they increased. In the fed wild type, ghrelin levels decreased. Conclusions: GHRP-2 stimulates GH in lit/lit mice and thus may be only partially GHRH-dependent in releasing GH in vivo. Alterations in peripheral plasma levels of the orexigenic ghrelin hormone in the fasting and fed state might indicate novel regulation of ghrelin secretion. **Supported by:** FAPESP, CNPq

06.009

GERMLINE MUTATION IN THE *ARYL HYDROCARBON RECEPTOR INTERACTING PROTEIN* (*AIP*) GENE IN FAMILIAL ACROMEGALY

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Context: Acromegaly is usually sporadic, but familial cases occur in association with several familial pituitary tumor syndromes. Recently, mutations in the *aryl hydrocarbon receptor interacting protein* (*AIP*) gene were associated with familial pituitary adenomas predisposition (PAP). **Objective:** To investigate the status of *AIP* in a pituitary tumor predisposition family. **Settings:** Non-profit academic center and medical centers. **Patients:** Eighteen members of a Brazilian family with acromegaly were studied. **Results:** A novel germline mutation in the *AIP* gene, Y268X, predicted to generate a protein lacking two conserved domains, was identified in four members of this family: two siblings with early onset acromegaly; a third, 41-year old sibling with a microadenoma but no clinical features of disease and his 3 year-old son. No changes were found in 14 unaffected at-risk relatives or in 92 healthy controls. **Conclusions:** We confirm the role of the *AIP* gene in familial acromegaly. This finding increases the spectrum of molecular defects that can give rise to pituitary adenoma susceptibility. Establishment of genotype-phenotype correlations in AIP mutant tumors will determine whether *AIP* screening can be used as a tool for clinical surveillance and genetic counseling of families with pituitary tumor predisposition. The underlying basis for the phenotypic variation within *AIP*-mutant families and the mechanism of AIP-mediated tumorigenesis remain to be defined. **Supported by:** FAPESP, CNPq e FFM

06.010

METÁSTASE HIPOFISÁRIA DE CARCINOMA PULMONAR COMO PRIMEIRA MANIFESTAÇÃO CLÍNICA – RELATO DE CASO.

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Introdução: Metástase para a região hipofisária é um evento raro, e na maioria das vezes a neuro-hipófise é o lugar mais afetado. Os tumores com maior freqüência de metástase para a região selar são: mama (47%), pulmão (19%), trato gastro-intestinal (6%) e próstata (6%). Em 80% dos casos a metástase é diagnosticada durante ou após a localização do sítio primário. **Relato de caso:** Paciente masculino, 49 anos, branco, com quadro de fraqueza, alteração progressiva da memória, cefaléia retro-orbitária, poliúria e polidipsia há sete meses e diminuição da libido há dois meses. Relatava de antecedentes pessoais: tabagismo, uso prévio de drogas inalatórias e endovenosa, era portador de hepatite B e C. Ao exame físico apresentava sinais de hipogonadismo e diminuição do campo visual bilateralmente. Exames hormonais evidenciaram hipopituitarismo, com deficiência de todos os eixos hipofisários, e foi diagnosticado Diabetes Insípidus (DI) pelo teste de jejum hídrico. Tomografia Computadorizada (TC) de crânio mostrou massa em região selar com extensão supra-selar a direita medindo 2,4 X 2,6 cm. Na Ressonância Nuclear Magnética (RNM) de hipófise verificou-se a mesma imagem, mas com invasão do terceiro ventrículo, intenso realce pós-contraste, e edema do parênquima encefálico adjacente.Os diagnósticos diferenciais da massa selar tiveram como hipóteses: tumores de células germinativas (TCG), doenças infiltrativas (Sarcoidose, Histiocitose), inflamatórias e infecciosas. A biópsia da lesão selar foi não conclusiva por escassez de material. RNM de neuro-eixo encontrou lesão lítica em L5 e a cintilografia óssea revelou várias áreas de hipercaptação em todo o esqueleto. O raio-x de tórax apresentou infiltrado intersticial que na TC mostrou tratar-se de múltiplos nódulos e um nódulo maior medindo 1,8 cm localizado perifericamente no lobo médio a D. Realizada biópsia óssea que revelou metástase de carcinoma de pulmão. Foi então, realizada imuno-histoquímica específica para carcinoma pulmonar no escasso material da biópsia da massa selar que mostrou ser positiva para tais marcadores. Paciente foi submetido a quimioterapia apresentando complicações infecciosas e evoluindo a óbito 4 meses após o diagnóstico. Discussão: Descrevemos um paciente com metástase hipofisária de carcinoma pulmonar como primeira manifestação clínica. A ausência de manifestações referentes ao sitio primário da doença, dificultou o diagnóstico precoce. Enfatizamos que apesar de rara, a metástase para hipófise deve ser lembrada em todas as lesões selares, principalmente quando na RM houver sinais de edema do parênquima encefálico adjacente ao tumor, e/ou estiver associada o DI. **Bibliografia:** (1) Fassett, D.R. Neurosurg Focus 16: E8, 2004. (2) Heshmati, H.M. Endocrinologist 12: 45, 2002. (3) Mussolino, L.R.C. In Vilar L et al (eds). Endocrinologia Clínica (3ªed): 1, 2006.

06.011

DOPAMINE AGONIST TREATMENT RESPONSE BEFORE AND AFTER MACROPROLACTINOMA SURGERY

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Introduction: Several theories are currently been used to explain dopamine agonist treatment failure in patients with prolactinomas. In general this failure is assumed on the basis of clinical goals, serum prolactin levels and reduction of the tumoral size. Treatment strategies in these situations include choosing the most tolerable dopamine agonist medication and dose increasing until adverse side effects are detected. Transesphenoidal surgery approach is sometimes an alternative option. There are a number of potential mechanisms to explain dopamine agonist therapy resistance, such as decreased number of tumoral D2 receptors, D2 receptor affinity and altered transduction signaling within tumor. **Case report:** A 42-year-old white man was admitted with a 1-year history of left visual field impairment. He did not complain of reduced libido nor had galactorrhea on physical exam. Serum prolactin (Prl) level was 6885 ng/mL. Bromocriptin doses was adjusted and titrated to 15 mg/day, but Prl levels remained high (910 ng/mL) with partial visual amelioration. It was then decided to change to carbegoline 3,5mg/week. After 6 months, despite a reduction in serum Prl to 322 ng/mL, a mild tumor size decreased was seen and on that occasion a transesphenoidal surgery was performed. The tumor was partially resected with mild improvement of the visual complaints. The Prl level 3 weeks after surgery was 82 ng/mL and 5 months after on carbegoline therapy Prl level reduced to 8.6 ng/mL with significant reduction in tumor remnant size. **Discussion:** In this case report we demonstrated different responses of dopamine agonist medication before and after surgery for macroprolactinoma. We speculate this pharmacologic pattern of drug-resistance might be attributed a global reduction on tumoral size. More studies, however, with larger number of cases are needed to address this question. **References** (1) Colao A et al. J Clin Endocrinol Metab 85:2246, 2000. (2) Delgrange, E et al. Clin Endocrinol 64:456, 2006. (3) DiSarno, A et al. J Clin Endocrinol Metab 86:5256, 2001. (4) Molitch, ME. Pituitary 8:43, 2005. (5) Webster, J et al. N Engl J Med 331:904, 1994.