Neuroendocrinology and Pituitary

CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

Long-Term Management and Successful Pregnancy of a Patient with a TSH Secreting Macroadenoma Treated with Octreotide

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SAT-253

Introduction: TSH-secreting pituitary adenomas (TSHomas) are the rarest form of pituitary tumors. Transsphenoidal surgery is usually the treatment of choice, although somatostatin analogs (SSAs) are a reasonable and effective option. Pregnancy in the setting of TSHomas is an even rarer situation, scarcely reported in the literature. We report the long-term management of a TSHoma treated with octreotide who developed a successful pregnancy.

Case Report: A 16 year-old girl was diagnosed in 2003 with a TSHoma after presenting with goiter, weight loss, tremors and headache. Laboratory tests showed central hyperthyroidism: TSH 2,78 uUI/ml (0,27-4,02); T4 22,4 ng/dl (4,8-12,7); T3 430 ng/dl (72-170) and pituitary MRI showed a 2 cm adenoma. TRH test showed a blunted response, and TSH did not suppress after T3 test, with hormonal values returning to normal range after octreotide administration. Since 2003 the patient have been treated with Octreotide LAR 20 mg. At 34 years-old she expressed her willingness to become pregnant. At this time, hyperthyroidism was controlled (TSH 1.79; T4 12; T3 181) and the pituitary adenoma was smaller (1.2 cm) while on octreotide LAR 20 mg every 8 weeks. Before conceiving, she did a visual field test that was normal and measured α-subunit (αSU), which was slightly increased (0.73 ug/l, upper limit of normal [ULN] < 0.6 ug/l). After 3 months, she successfully conceived. During first trimester, thyroid function remained controlled. The patient was asymptomatic and the fetus was developing as expected. From 18 weeks on, T3 started to increase (T3 227 ng/dl– ULN 200 ng/dl) with normal T4 and FT4 and without symptoms or fetal repercussion. Alpha-subunit increased to 9.5 ug/l. Throughout pregnancy, octreotide was administered in the same pre-pregnancy dosage. At 37 weeks, αSU was 272.314 ug/l after 1:100 dilution (ULN < 604 ug/;) and HCG was 38.316. The patient developed gestational diabetes mellitus that was managed with diet counseling. Spontaneous delivery occurred at 39 weeks, birth weight was 3160g, APGAR 9/10. Newborn thyroid function was normal. Three months after delivery, the patient complained of hand tremors and hair loss. New laboratory tests revealed TSH 6,7 uUI/ml (ULN <4.5); T4 12,9 (ULN <12); T4L 3,3 (ULN <1.7); T3 247 (ULN <200) and αSU was 513 ug/l (ULN< 0.6). Octreotide LAR 20 mg interval was decreased to every 6 weeks. Currently, ten months after delivery, the patients is asymptomatic and thyroid function is normal.

Conclusion: TSHoma appears to be safely managed throughout pregnancy without the need of stopping octreotide, which seems not to adversely affect outcomes for the mother and the fetus. This case also illustrates the long-term management (16 years) of TSHoma with octreotide with excellent hormonal and structural response.

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PITUITARY TUMORS II

IGF-I Variability and Its Association with Demographic and Clinical Characteristics in Patients with Acromegaly Treated with Injectable Somatostatin Receptor Ligands (SRLS); Results from an International Prospective Phase III Study

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Abstract: **Background:** In clinical practice, most patients responding to injectable somatostatin receptor ligands exhibit IGF-I variability around the upper limit of normal (ULN) during long-term follow up. These fluctuations are thought to result from various factors such as assay variability, nutrition, comorbid conditions, concomitant medications and other unknown factors. The magnitude of this variability, and the factors affecting it, is not well understood in patients with acromegaly treated with injectable SRLs. **Methods:** IGF-I levels of patients responding to and stably treated with injectable SRLs were measured over time in the CHIASMA OPTIMAL phase III study. Two time periods were assessed - Period 1, three assessments during screening phase before randomization to octreotide capsules (N=56), and Period 2 - multiple assessments up to week 36, in patients rescued with SRL injections for at least 12 weeks (N=21). The time from the last injection to each of the 3 assessments in period 1 [Screening visits 1 and 2 (SV1 & SV2), and Baseline (BL)], was on average 6.8 ± 10.7 (SD), 15.8 ± 2.7, and 29.0 ± 1.8 days respectively. Correlation with various demographics and Baseline characteristics, including age, gender, weight, BMI and residual tumor size to IGF-I variability was assessed. Percent change for each individual patient from Minimal to Maximal IGF-I values within each period was computed and the overall population mean was calculated (lowest value was used as the denominator and all other values were expression as a positive % above this value). **Results:** The overall mean within-patient percent change of IGF-I levels during Period 1 was 20.48 ± 15.56 (range: 0.6-81). Mean IGF-I levels for SV1, SV2 and BL were 0.78 ± 0.18, 0.79 ± 0.18, and 0.85 ± 0.22 x ULN respectively. The overall increase in mean IGF-I levels from SV1 to BL (longest time interval) was statistically significant (p=0.0002; paired T-test). Analysis

of IGF-I levels in patients during Period 2, revealed that the overall mean within-patient percent change of IGF-I levels was 15.27 ± 12.20 (range: 0-41.5). The mean duration of follow up during this period, after patients were already treated for ≥12 weeks with injectable SRL, was 1.72 (± 1.29) months. The variability observed in Period 2 was similar to that observed in the entire sample evaluated in Period 1. No significant differences were found in the mean IGF-I percent change between any demographic or baseline characteristic subgroup examined. **Conclusion:** IGF-I levels fluctuate in patients with acromegaly who are responsive to injectable SRLs. These fluctuations are wide and can be up to 81% higher than the lowest (most controlled) value, with an average increase of approximately 20%. Significant IGF-I increases were observed at the end of the long acting SRL injection interval.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS II

Bisphosphonate and Denosumab Refractory Hypercalcemia of Malignancy: What Else Is at Play?

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Hypercalcemia of Malignancy has been historically responsive to anti-resorptive agents. However, when multiple mechanisms contribute, it may be difficult to treat with one modality. This case highlights the importance of the work up in treatment of hypercalcemia in a low PTH state. A 44 yo M with h/o high grade metastatic spindle cell neoplasm with skeletal metastasis was admitted with hypercalcemia. He reported some constipation prior to presentation, however denied confusion. His vital signs were notable for HR of 86 bpm and BP of 112/75 mmHg. Labs at admission were remarkable for an uncorrected Ca of 16.1 (8.8-10.3 ng/mL), a phosphorus (Phos) level of 3.3 mg/dL (2.5-4.5 mg/dL), a PTH level of 11 pg/mL (15-65 pg/mL), PTHrP level of 134 pg/mL (14-27 pg/mL), a 25 OH vit D level of 11 ng/mL (30-100 ng/mL), and a BUN/Cr and GFR of 34/2.38 (8-22 mg/dL/0.5-1.3 mg/dL) and 32 ml/min/m2. He was given intranasal calcitonin and ergocalciferol, then received 2mg IV of zolendronic acid, which reduced the patient's Ca level to a nadir of 6.6 ng/mL in 5 days. On the next admission serum Ca was elevated to 15.7 ng/dL, which did not respond to zolendronic acid. Given that patient's Ca was refractory to zolendronic acid, denosumab was given but had no response. He then underwent surgery for cord compression and was given dexamethasone (dex) 4mg IV Q6h post-op. His Ca responded quickly to dex, with a nadir to 9.2 ng/dL, however his Ca became elevated after cessation. Given response to dex, vit D 1,25 OH level was sent and was elevated at 94 pg/mL (18-72 pg/mL). In addition, given his inappropriately normal Phos level in the setting of low PTH, FGF23 was sent and came back elevated at 473 RU/mL (<180 RU/mL). This was likely due to increased bone turnover and release of FGF23. He was discharged with a Ca level of 12.5 ng/mL, however was found to have an elevated Ca to 14.9 ng/mL on presentation to clinic. Given concern that Vit D 1,25 OH, PTHrP and direct bony involvement were all contributing to his hypercalcemia, patient was started on IVF and dex IV. His calcium responded 11.5 ng/mL and was then transitioned to PO dexamethasone and plaquenil. The most likely explanation for this phenomenon is malignancy induced cytokine/PAMP release, which stimulates 1-alpha hydroxylase in tumor macrophages to convert 25 OH D to 1,25 OH D. This was supported by his elevated 1,25 OH D level and a decreased 25 OH D, which suggests that 25 OH D was used as substrate by activated macrophages. This case highlights the importance of ancillary work up of hypercalcemia when a patient's calcium is refractory to standard anti-resorptive therapy. Moreover, it shows the need for a systematic approach when treating hypercalcemia.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Musashi Exerts Translational Control Within Anterior Pituitary Cells of the POU1F1 Lineage.

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The activation of transcription factor *Pou1f1* at embryonic day 13 gives rise to the pituitary populations of somatotropes, lactotropes, and thyrotropes and these populations maintain expression of *Pou1f1* throughout life. The Musashi family of RNA regulatory proteins is known to regulate stem cell fate by repressing translation of target mRNAs needed for differentiation. Previously our lab has shown that female *Lepr*-null somatotropes have reduced POU1F1 protein levels but do not have changes in *Pou1f1* mRNA expression. Stimulation with leptin increased the POU1F1 protein levels 3-fold, but did not change *Pou1f1* mRNA suggesting a post-transcriptional mechanism for leptin's regulation of *Pou1f1*. An *in silico* analysis indicated the presence a number of potential regulatory elements (MBEs) within the *Pou1f1* mRNA 3' UTR, including 8 consensus Musashi binding elements. Interestingly, we found *musashi* mRNA and protein levels were increased in *Lepr*-null somatotropes. This suggested that leptin regulates the expression of *musashi* in somatotrope populations and may be a candidate translational regulator of the *Pou1f1* mRNA. We verified that MSI binds directly to the *Pou1f1* mRNA 3' UTR MBEs by EMSA *in vitro* and exerts translational repression (using reporter mRNA assays in transfected cell populations). Single cell RNA sequencing of pituitary cells from control male and female mice indicates that *MSI* and *Pou1f1* mRNAs are co-expressed in somatotropes, lactotropes as well as thyrotropes. Immunocytochemical analyses confirmed that Musashi protein is present in mixed and purified somatotrope populations. Furthermore, immunoprecipitation with Musashi1 antibody showed a 5-fold enrichment of *Pou1f1* mRNA in control female