Pituitary adenomas and menopause

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Clinical case 1

- 38-year-old patient referred for exploration of premature ovarian failure
- Secondary amenorrhea for 6 months
- Family history of precocious menopause in her mother at the age of 39
Clinical case 1

Clinical examination:
- H=1.65m, W=70 kg
- BP=120/80mmHg, pulse=80bpm
- Bilateral galactorrhea on mammary gland examination
- Complaints: «migraines» aggravated during the last 6 months, very tired, cannot lose weight
Clinical case 1

Biology:
- FSH=5 U/l
- LH=8 U/l
- Estradiol=30 ng/l
- PRL= 50 ng/dl (N:4.7-23.5)
- MacroPRL negative
- TSH=10mU/l (N: 0.20-4.20)
- fT4=9pg/ml (N: 9.0-17.0)
Clinical case 1

Thyroid US: hypoechogenic structure, slightly increased vascularisation, absence of nodules, corresponding to a thyroiditis

Anti-TPO – 600 UI/ml (N<34)

-> 75ug of L-thyroxine/day
Clinical case 1

3 months later:
- Feeling less tired, but still amenorrhea
- Persistance of headaches

Biology:
- TSH=2.5 mU/l
- FSH=7 U/l
- LH=10 U/l
- Prolactine=70 ng/ml
Pituitary MRI: left pituitary macroadenoma of 16mm largest diameter, without invasion of the cavernous sinus or optic chiasm compression.
Clinical case 1

Cabergoline: 1/2cp/week, then 1/2cp x 2/week with size reduction of the adenoma
Clinical case 1

- 3 years later -> menopause while still on cabergoline
- Therapeutic window: after 6 months, PRL is again high (60 ng/dl)
- MRI: persistence of a left adenoma residue
Clinical case 1

Why continue cabergoline?
- Risk of increase of volume of adenoma
- Increased risk of breast cancer due to chronically elevated prolactin levels
Plasma Prolactin Concentrations and Risk of Postmenopausal Breast Cancer

Shelley S. Tworoger,1,2 A. Heather Eliassen,1,2 Bernard Rosner,1,3 Patrick Sluss,4 and Susan E. Hankinson1,2

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...1.02–1.76; P-trend = 0.01]. The association differed by estrogen receptor/progesterone receptor status (P-heterogeneity = 0.03). The relative risk was 1.78 (95% CI, 1.28, 2.50; P-trend < 0.001) for estrogen receptor+/progesterone receptor+, 0.76 (95% CI, 0.43, 1.32; P-trend = 0.28) for estrogen receptor+/progesterone receptor−, and 1.94 (95% CI, 0.99, 3.78; P-trend = 0.12) for estrogen receptor+/progesterone receptor− breast cancers. Associations generally were similar for ductal and lobular carcinomas (P-heterogeneity = 0.43) and by tumor size (P-heterogeneity = 0.24). Among estrogen receptor+/progesterone receptor+ cancers, the association did not significantly differ by postmenopausal hormone use, years between blood draw and diagnosis, or after adjustment for estradiol (relative risk, 1.93; 95% CI, 1.16, 3.22; P-trend = 0.01). Our prospective data suggest that plasma prolactin concentrations are associated with an increased risk of postmenopausal breast cancer, particularly for estrogen receptor+/progesterone receptor+ cancers, and independently of estradiol.
Prolactin and Breast Cancer Etiology:
An Epidemiologic Perspective

Shelley S. Tworoger • Susan E. Hankinson

lactin and risk. In a pooled analysis of ~80% of the world’s prospective data, the relative risk (RR) comparing women in the top vs bottom quartile of prolactin levels was 1.3 (95% confidence interval (CI): 1.1, 1.6, \( p \)-trend=0.002). The results were similar for premenopausal and postmenopausal women. Most notably, high prolactin levels were associated with a 60% increased risk of estrogen receptor (ER) positive tumors, but not with ER negative tumors. Limited genetic data suggest a role of polymorphisms in the prolactin and prolactin receptor genes in risk of breast cancer. Studies of survival have suggested that high pretreatment prolactin levels were associated with treatment failure, earlier recurrence, and worse overall survival. Parity and certain medications are the only confirmed factors associated with prolactin levels in women. Overall, epidemiologic data suggest that prolactin is involved in breast
Clinical case 2

- 48-year old patient addressed for secondary amenorrhea
- Symptoms of fatigue, headache and visual disturbance, but ophtalmologist says she needs a new prescription
- She is wondering if it isn’t the menopause causing her these symptoms, but hasn’t experienced hot flashes yet
Clinical case 2

Biology:
- FSH = 50 U/l
- LH = 3.5 U/l
- Estradiol < 12 ng/l
- Progesterone < 0.15 ug/l
- Prolactine = 60 ng/dl (N: 4.7-23.5)
- Cortisol = 100 ug/l at 8am (N: 100-250)
Clinical case 2

Pituitary MRI: large adenoma with suprasellar extension compressing the optic chiasm, invading the sphenoid sinus and the left cavernous sinus.
Clinical case 2

- **Treatment:**
  - Trans-sphenoidal surgery of the macroadenoma
  - Anatomo-pathology: pituitary adenoma with intense IHC staining for FSH
Clinical case 2

- **Follow-up:**
- After surgery the patient presents a persistent gonadotroph pituitary insufficiency
- She complains of vaginal dryness and dyspareunia
High Prevalence of Pituitary Adenomas: A Cross-Sectional Study in the Province of Liège, Belgium

Adrian F. Daly, Martine Rixhon, Christelle Adam, Anastasia Dempegioti, Maria A. Tichomirowa, and Albert Beckers

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Total population = 71972 individuals

3 provinces: Oupeye, Soiron, Ans-Alleur

Prevalence of pituitary adenomas:

1:1064

THE “ADENOMA VALLEY”
Prevalence of pituitary adenomas

High Prevalence of Pituitary Adenomas: A Cross-Sectional Study in the Province of Liège, Belgium

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- Prolactinomas - 66%
- Non-fonctionning adenomas - 14.7%
- GH-secreting adenomas - 13.2%
- Cushing disease – 5.9%
- 9 women were diagnosed at >50 years
Prevalence of pituitary adenomas

Clinical Endocrinology (2010) 72, 377–382

Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK)

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Fig. 1  Distribution of the pituitary adenomas subtypes.
What is FIPA?

- Familial cause of pituitary adenomas
- All phenotypes possible
- Heterogeneous – Homogeneous families
- More aggressive than sporadic cases
- Etiology unknown in 70 - 85% of cases
Homogeneous FIPA families: Proportions by Phenotype

- Somatotropinoma: 58.4%
- Prolactinoma: 32%
- NFPA: 7.2%
- Others: 2.4%
- Cushing's disease: 1.6%
- Gonadotropinoma: 0.8%
Heterogeneous FIPA families: Proportions by Phenotype

- GH-NFPA; 16.9
- GH-PRL-NFPA; 8.4
- Others, 10.8
- GH-PRL; 42.2
- PRL-NFPA; 21.7
- GH-LH/FSH; 1.2
- GH-TSH; 2.4
- PRL-ACTH; 2.4
- PRL-LH/FSH; 1.2
- NFPA-ACTH; 1.2
- GH-PRL-LH/FSH; 1.2
- GH-PRL-ACTH; 1.2

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- GH-TSH; 2.4
- PRL-ACTH; 2.4
- PRL-LH/FSH; 1.2
- NFPA-ACTH; 1.2
- GH-PRL-LH/FSH; 1.2
- GH-PRL-ACTH; 1.2
FIPA and *AIP* mutations

- In 15-20% of cases: *AIP* mutation (50% in FIPA with homogeneous GH adenoma presentation)

- *AIP* + all phenotypes but more frequently GH

- FIPA *AIP* + more aggressive than FIPA *AIP* –

- FIPA *AIP* + less responsive to therapeutics
At risk groups for AIPmut

- 0-4% of unselected sporadic adenomas
- ~30% gigantism
- 15-20% FIPA
- 11% of sporadic macroadenomas <30yr
- 9-20% children with pituitary adenomas

Beckers A et al, Endocrine Review 2013
Clinical Characteristics and Therapeutic Responses in Patients with Germ-Line AIP Mutations and Pituitary Adenomas: An International Collaborative Study

Adrian F. Daly,* Maria A. Tichomirowa,* Patrick Petrossians,* Elina Helledaa,* Marie-Lise Jaffrain-Rea, Anne Barlier, Luciana A. Naves, Tapani Ebeling, Auli Kauru, Antti Raapana, Laure Cazabat, Ernesto De Menis, Carmen Fajardo Montanana, Gerald Raverot, Robert J. Weil, Timo Sane, Dominique Maier, Sebastien Nogger, Maria Yaneva, Antoine Tabarin, Elisa Verrua, Elia Eioranta, Arnaud Murat, Outi Vienmäa, PasI. Salmela, Philippe Emy, Rodrigo A. Toledo, Maria Isabel Sabaté, Chiara Villa, Marc Popelier, Roberto Salvatori, Juliet Jennings, Ángel Fernández Llongas, José Ignacio Labarta Aizpún, Maripanti Georgitsi, Ralf Paschke, Cristina Ronchi, Matti Valimaki, Coreda Salortana, Wouter De Herder, Renato Cozzi, Mirtha Guiterman, Flavia Mavig, Maria Stefania Lagorigno, Georges Halaby, Vinciane Corman, Marie-Thérèse Hagelstein, Jean-François Vanbellinghen, Gustavo Barcelos Barra, Anne-Paula Gimenez-Roqueplo, Fergus J. Cameron, François Borson-Chazot, Ian Holdaway, Sergio P. A. Toledo, Günter K. Stalla, Anna Spada, Sabina Zachariewa, Jerome Bertherat, Thierry Brue, Vincent Bours, Philippe Chanson, Lauri A. Aaltonen, and Albert Beckers*

Results: The AIPmut population was predominately young and male (63.5%); first symptoms occurred as children/adolescents in 50%. At diagnosis, most tumors were macroadenomas (93.3%); extension and invasion was common. Somatotropinomas comprised 78.1% of the cohort; there were also prolactinomas (n = 13), nonsecreting adenomas (n = 7), and a TSH-secreting adenoma. AIPmut somatotropinomas were larger (P = 0.00026), with higher GH levels (P = 0.00068), more frequent extension (P = 0.018) and prolactin cosecretion (P = 0.00023), and occurred 2 decades before controls (P < 0.000001). Gigantism was more common in the AIPmut group (P < 0.000001). AIPmut somatotropinoma patients underwent more surgical interventions (P = 0.00069) and had lower decreases in GH (P = 0.00037) and IGF-I (P = 0.028) and less tumor shrinkage with somatostatin analogs (P < 0.00001) vs. controls. AIPmut prolactinomas occurred generally in young males and frequently required surgery or radiotherapy.

Conclusions: AIPmut pituitary adenomas have clinical features that may negatively impact treatment efficacy. Predisposition for aggressive disease in young patients, often in a familial setting, suggests that earlier diagnosis of AIPmut pituitary adenomas may have clinical utility. U Clin Endocrinol Metab 95: E373–E383, 2010
Thank you for your attention!

Igor Morski, Nature series