Published in final edited form as:

Lancet. 2015 January 24; 385(9965): 392. doi:10.1016/S0140-6736(14)62294-7.

Ovarian hyperstimulation from ectopic FSH hypersecretion

Alexander D Miras^{#1}, Julia Mogford^{#1}, John Wright^{#1}, Nigel N Mendoza², Paraskevi Xekouki³, Amish Lakhani², Natalia S Pellegata⁴, Costantine Stratakis³, Federico Roncaroli^{#2}, and David Russell-Jones^{#1}

¹Cedar Centre, Royal Surrey County Hospital, Guildford, GU27XX

²Neuroradiology, Neurosurgery and Neuropathology, Imperial College London, London

³Section of Endocrinology and Genetics, National Institute of Health, Bethesda, USA

⁴Institute of Pathology, Helmholtz Zentrum München, Neuherberg Germany

These authors contributed equally to this work.

Case report

A previously healthy nulliparous 26-year-old Caucasian woman presented to the emergency department in May 2009 with pelvic pain, abdominal distension and vomiting. Pelvic ultrasonography showed enlarged ovaries containing multiple cysts. Ovarian hyperstimulation syndrome (OHS) was diagnosed and the patient recovered swiftly with rehydration, antiemetics and analgesia. As she was not on fertility treatment or medications she was referred to the endocrinology clinic. She reported a one-year history of amenorrhoea following cessation of the oral contraceptive, episodes of pelvic pain, flushing and vomiting. Her previous medical history and physical examination were unremarkable. Family history was incomplete as she is an adopted child. Initial investigations revealed a consistently elevated plasma follicle-stimulating hormone (FSH checked three times: 32, 26 and 32 iu/L respectively, follicular phase normal range 2.5-10.2 iu/L), a markedly elevated oestradiol (>3000 pmol/L, follicular phase normal range 72-530 pmol/L) and a suppressed luteinising hormone (LH <1 iu/L, follicular phase normal range 1.9-12.5 iu/L). The other pituitary axes were intact and urine 5-hydroxyindoleacetic acid concentration was within the normal range. Neither FSH nor LH rose in response to LH-releasing hormone stimulation. A FSH secreting pituitary adenoma was therefore suspected. A dedicated pituitary MRI indeed revealed a 0.5 cm adenoma (Figure 1A). She was therefore referred for transsphenoidal surgery, which she underwent uneventfully.

Unexpectedly, the levels of plasma FSH did not drop after surgery. Histopathological examination of pituitary tissue revealed an adenoma composed of growth hormone and

Corresponding author: Dr John Wright, Cedar Centre, Royal Surrey County Hospital, Guildford, GU27XX, (john.wright5@nhs.net), Telephone number: 01483 571122.

Contributors

ADM, JW, NNM, AL, FR and DRJ managed the patient. PX, NSP and CS performed the genetic analyses. All authors contributed to the writing of the report.

Conflict of interest statement

The authors declare no conflicts of interest relevant to this report.

prolactin cells. Immunostains for FSH, LH and steroidogenic factor 1 did not reveal any gonadotroph component (Figure 1). Ten days post-operatively, the patient was readmitted with severe pelvic pain, vomiting and lactic acidosis. An urgent abdominal and pelvic CT-scan demonstrated torsion and infarction of the right ovary, but also revealed a solid 4.5×7.5cm mass arising from the body of the pancreas (Figure 2A). In view of the severity of her presentation, she underwent an emergency laparoscopic right salpingo-oophorectomy and a central pancreatectomy with Roux-en-Y reconstruction. Pathological examination showed a well-differentiated pancreatic neuroendocrine tumour (NET) expressing FSH β -subunit and the common α -subunit (Figure 2) (FSH is a heterodimer hormone composed of a specific β -subunit and the α -subunit which is common between FSH, LH and TSH). Necrosis was absent, mitotic count was 1×50HPFs and the Ki67 labelling index was lower than 1%. No mutations of *MEN1*, *SDHA*, *SDHB*, *VHL*, *CDKN1B* and *CDKN2C* genes were identified in the genomic DNA. Menstrual cycle and FSH normalised in a few months after surgery further indicating that the pancreatic mass was the source of FSH hypersecretion and the cause of OHS. In July 2014 the patient was well, took no medication, and there was no evidence of recurrence of either tumours.

This case demonstrates that incidental tumours in endocrine organs, including the pituitary, are common, can lead to an erroneous interpretation of hormonal hypersecretion and unnecessary surgical procedures (1). In the vast majority of cases, OHS is a complication of fertility treatments. Less commonly, it is associated with excessive production of FSH from a pituitary gonadotroph adenoma (2) and rarely from a lung NET (3, 4). Pancreatic NETs are also rare and usually non-functioning. They are therefore found incidentally or present with signs and symptoms of compression. Prognosis depends on the patient's age and the tumour's grade and stage. Similar to patients with Cushing's syndrome, pre-operative inferior petrosal sinus sampling should have probably been performed to localise the source of FSH but this procedure is invasive and not commonly used given the exceptional occurrence of ectopic FSH secretion. In conclusion, this case illustrates the importance of a broad differential diagnosis in patients presenting with signs and symptoms of hormone hypersecretion.

References

1. Scangas GA, Laws ER, Jr. Pituitary incidentalomas. *Pituitary*. 2013.
2. Roberts JE, Spandorfer S, Fasouliotis SJ, Lin K, Rosenwaks Z. Spontaneous ovarian hyperstimulation caused by a follicle-stimulating hormone-secreting pituitary adenoma. *Fertility and sterility*. 2005;83(1):208–10. [PubMed: 15652911]
3. Burgos J, Cobos P, Vidaurrezaga N, Prieto B, Ocerin I, Matorras R. Ovarian hyperstimulation secondary to ectopic secretion of follicle-stimulating hormone. Literature review prompted by a case. *Fertil Steril* 2009;92(3):1168.e5–8. doi: 10.016/j.fertnstert.2009.06.023. Epub Jul 15.
4. Sardella C, Russo D, Raggi F, Lombardi M, Urbani C, Brogioni S, et al. Ectopic expression of FSH receptor isoforms in neoplastic but not in endothelial cells from pancreatic neuroendocrine tumors. *J Endocrinol Invest* 2013;36(3):174–9. doi: 10.3275/8472. Epub 2012 Jun 25. [PubMed: 22732316]

Figure 1:
Pituitary imaging and histology.

Axial (**A**) post-contrast T1-weighted magnetic resonance imaging sequence demonstrates an enhancing nodule in the central and left side of the pituitary resulting in some distortion of its superior contour and modest infundibular deviation to the right (arrow). Pituitary adenoma is composed of eosinophilic cells (**B**, HE $\times 40$) expressing growth hormone (**C**, immunoperoxidase $\times 20$) and prolactin (**D**, immunoperoxidase $\times 20$); the immunoreaction for FSH β -subunit is negative (**E**, immunoperoxidase $\times 20$).

Figure 2:

Abdominal computer tomography scan (A) demonstrates a large lesion involving the head of the pancreas (arrow); the tumour is well-demarcated and shows a yellow, lobulated cut surface (B) with compressive margin (C, HE – ×4). The lesion is mostly composed of trabeculae and perivascular pseudorosettes of mildly atypical cells with faintly eosinophilic cytoplasm (D, HE ×20); neoplastic cells are positive FSH β -subunit (E, immunoperoxidase – ×20).