

Multi-Drug Resistant Hyperprolactinaemia

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INTRODUCTION

- Hyperprolactinaemia is the most common endocrine disorder of the hypothalamic-pituitary axis. Dopamine agonists (DA) are the treatment of choice for the majority of patients – most commonly used are Bromocriptine, Cabergoline, Pergolide and Quinagolide.
- A subset of patients with hyperprolactinaemia (due to a prolactin-secreting pituitary tumour), however, are resistant to DA therapy. Resistance is defined by a failure to achieve normal prolactin levels on maximally tolerated doses of DAs and/or failure to achieve a 50 % reduction in tumour size.^[1]
- Management of resistant microprolactinomas can be challenging. We describe a case of multi-drug resistant hyperprolactinaemia in a young patient trying to conceive.

CASE

A 22-year-old female first presented to our endocrine clinic in 2008 with a six-month history of galactorrhoea and irregular menses.

- She was noted to have hyperprolactinaemia (prolactin: 2401mIU/L) with a negative macroprolactin screen.
- Cabergoline was commenced and gradually increased to 1mg daily due to poor response to therapy.
- Besides one serum prolactin of 486mIU/L, prolactin levels remained persistently >1000mIU/L.
- She reported good concordance with medication.
- She was then switched to Bromocriptine in 2012 and titrated to a maximum dose of 15mg with no biochemical or clinical response.
- Treatment with Quinagolide (up to 150 mcg od) was also tried, but was poorly tolerated (headaches and nausea). Again this was unsuccessful in lowering serum prolactin levels.
- Pergolide was discussed, but was not tried.

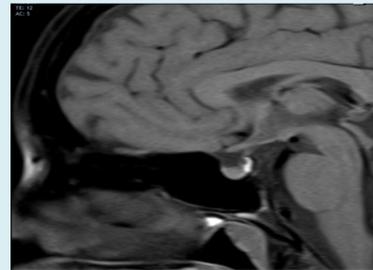
INVESTIGATIONS

- ↳ Her cannulated prolactin levels were >1500 mIU/L.
- ↳ Reverse FSH:LH ratio.
- ↳ Pelvic ultrasound: normal endometrial thickness (no polycystic ovaries)
- ↳ Initial pituitary MRI scan: 4mm microadenoma.
- ↳ Subsequent MRIs: no radiological evidence of microadenoma.

Cortisol	289 nmol/L
TSH	3.51 mIU/L
fT4	15.9 pmol/L
fT3	4.7 pmol/L
LH	18.8 IU/L
FSH	8.1 IU/L
Oestradiol	239 pmol/L
Testosterone	2.0 nmol/L
SHBG	40 nmol/L
IGF-1	20.4 nmol/L
Prolactin	2401 mu/L

FOLLOW-UP

- Resistance to drug therapy was confirmed by admitting the patient to hospital where she received medication under supervision and despite this, her serum prolactin did not decline.
- Two further MRI scans in 2013 and 2015 did not demonstrate a pituitary microadenoma, despite elevated prolactin levels.



- The patient is currently taking no DA therapy. Her latest prolactin is 1656mIU/L, she menstruates 4 times a year and continues to experience galactorrhoea.
- She would like to conceive and has been referred to a fertility specialist.

CONCLUSION

- Our case highlights the challenges in the management of a multi-drug resistant microprolactinoma to three high dose DAs.
- Whilst this lady's microadenoma suitably shrunk in size, she has remained symptomatic with elevated prolactin levels.
- Reduction in tumour size but failure to normalise serum prolactin levels has been previously described.^[2]
- The suggested mechanism through which resistance is mediated is through the loss of pituitary D2 receptors, which occurs in both micro- and macro-adenomas.^[3]
- It is essential to exclude alternate causes such as non-compliance to therapy.
- Although treatment with surgery or radiotherapy may be considered in some patients, we feel the potential disadvantages of these therapies outweigh the benefits.

References:

- [1] Melmed S et al., Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab*, 2011;96:273–88.
 [2] Maiter D. Current Challenges in the Management of Prolactinomas. *Euro Endocrinol*, 2015;11(1):39–40
 [3] Olafsdottir et al. Management of resistant prolactinomas. *Nat Clin Pract Endocrinol Metab*, 2006; 2 (10), 552-561