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Menopause and prolactin secreting tumours

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ABSTRACT

Introduction

Prolactinomas without galactorrhea may be considered menopause or not diagnosed. This is a cases series.

Case1. 76-year female with menopause at age of 52 was discovered at 66 yrs with high prolactin and a pituitary micro-nodule. Bromocriptin was continued for 6 years then switched to cabergoline with constant imagery. The patient did not display at all galactorrhea. Osteoporosis was diagnosed at age of 66 with previous 2 fragility fractures.

Case2. 45-year female is known with secondary amenorrhea (without galactorrhea) for the last 7 years being considered menopause. She experienced headaches thus a MRI was performed and found a pituitary tumour of 1.5cm. Low FSH with increased prolactin was revealed. Cabergoline was started. Within 2 months the menses resumed and headache mildly improved. After 3 months prolactin normalised under weekly 2 mg of cabergoline. Periodical prolactin control is necessary as well as a pituitary scan at 6 months.

Case3. 39-year female had a 3 yrs history of secondary amenorrhea. A prolactin of 117ng/mL and a microprolactinoma of 0.77cm were found. Cabergoline was started and progressively increased up to 1.5mg per

week. The prolactin quickly normalised up to 8ng/mL within 4 months. She was followed for 2 years and the imagery found a tumour reduction to 0.44cm.

Conclusion

Prolactinomas associate a great variety of clinical presentations. They interfere with menopause by mimicking it in cases without galactorrhea. Also a newly diagnosed prolactinoma during menopause needs long term therapy and followed-up for especially for bone safety.

Keywords: prolactin, prolactinoma, menopause

Introduction

The prolactin secreting tumours also named prolactinomas represent the largest area of pituitary masses with an endocrine secretor profile and their frequency is actually increasing for the last decades thanks to better diagnosis tools as performing a routine prolactin assay in subjects with fertility issues or having a magnetic resonance imagery (MRI) either a computed tomography (CT) done in case of persistent headaches or visual field anomalies. [1,2,3] Once a diagnosis of prolactinoma has been established the therapy options vary from medication to surgery or radiotherapy although (opposite to the others secretor pituitary adenomas) the prolactinomas have as first line management the dopamine analogues. [4,5]

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This paper will point out several practical aspects in prolactinomas: first issue is related to the therapy options in menopausal women and the importance of continuing with dopamine agonists even at lowest efficient dose in postmenopausal years and secondary we will focus on long standing secondary amenorrhea misdiagnosed as menopause in women of reproductive age.

This is a cases series providing the medical history, the anamnesis data as well as hormonal panel and imagery scan information. The informed consent was obtained from each patient.

Cases presentation

Case presentation 1

76-year old non-smoker female with menopause at age of 52 has a history of high blood pressure, kidney stones, and she had some investigations done for a breast lump at age of 66. The breast tumour was benign based on biopsy report but a high serum prolactin performed under these circumstances was revealed (of mean 70 ng/mL with repeated high levels for several weeks, considering the normal ranges up to 20 ng/mL). A pituitary micro-nodule of 0.65 cm was confirmed and based on these the diagnosis of microprolactinoma was done. Therapy with daily bromocriptin was progressively introduced and the prolactin levels normalised within weeks from starting dopamine analogue therapy and after the very first year the pituitary computed tomography pointed a 30% volume reduction. (Figure 1) The bromocriptin was reduced to a minimum efficient dose to keep the levels of prolactin within the normal ranges. When tried to stop the therapy the hormone increased above the normal limit so the treatment was continued for 6 years with no side effects.

Later for practical reasons the bromocriptin was switched to cabergoline and kept to a minimum efficient dose of weekly 0.5 mg up to the present. The imagery data were constant under cabergoline therapy. Remarkably the patient did not display

galactorrhea at baseline neither during follow-up when resuming the dopamine agonist therapy with secondary hyperprolactinemia.



Figure 1. Contrast pituitary computed tomography in 66 year old female: right microadenoma (yellow arrow)

The patient also has a history of low trauma right wrist fracture at age of 56. She remained uninvestigated and untreated for osteoporosis and at age of 60 she suffered another wrist fragility fracture. Only when she came to an endocrinology evaluation for her hyperprolactinemia at age of 66 a central Dual X-Ray Energy Absorptiometry (DXA) was performed and osteoporosis score was found with the lowest T-score at left distal radius of -2.9 (associating a Z-score of -0.6 and a Bone Mineral Density of 0.505 g/cm²). A primary hyperparathyroidism was suspected based on DXA assay results and the renal stones crisis she previously had but the parathormone levels remained normal. She was put on weekly risendronate for 5 years with vitamin D and calcium supplements with no further incidental fractures.

Case presentation 2

45-year old non-smoker female is known with secondary amenorrhea (without galactorrhea) for the last 7 years. At first she was evaluated in a gynaecological centre and considered as menopause. No hormonal replacement therapy was started. During this time she started having headaches thus

cerebral and pituitary MRI was performed and found a pituitary tumour of 1.5 cm without mass effect. She was referred for an endocrinology check up.

Table I. Hormonal panel in 45-year old female with secondary amenorrhea for the last 7 years

Parameter	Level	Normal ranges	Units
FSH (Follicle Stimulating Hormone)	6.78	1.27-19.26	mIU/mL
Prolactin	204	3.34-26.72	ng/mL
TSH (Thyroid Stimulating Hormone)	1.89	0.5-4.5	μIU/mL
IGF1 (Insulin Growth Factor 1)	129	156-217	ng/mL
Morning plasma ACTH (adrenocorticotrophic hormone)	15.06	3-66	pg/mL
Plasma morning cortisol	16.53	6.2-19.4	μg/dL

On admission the biochemistry parameters as well as thyroid profile were normal and low FSH (for so called menopause) with increased prolactin was found. (Table I) The nadir GH (Growth Hormone) in oral glucose tolerance test was less than 0.05 ng/mL suggesting no GH co-secretion. Neither adrenal axes disturbances were found. (Table I) Low dose of cabergoline was started with twice weekly administration a progressive dose increase was recommended. Within 2 months the menses resumed and the headache mildly improved. After 3 months the prolactin levels got within the normal levels (of 13.33 ng/mL) while the patient was under weekly 2 mg of cabergoline. Periodic prolactin control is necessary as well as a pituitary scan at 6 months. The dopamine analogue dose will be progressively adjusted based on hormonal profile and imagery results.

Case presentation 3

39 - year old non smoking female had a history of secondary amenorrhea for 3 years. She did not take any medical control for this matter since apart from menses resumption (which she believed is menopause) she did not experience any others complains. Then she desired fertility so she presented to an endocrine evaluation. On admission (in 2013)

the clinical general and endocrine exam found no other anomaly. The endocrine panel of investigations included a prolactin level of 117 ng/mL (normal levels less than 21 ng/mL) and a FSH of 9 mIU/mL. A microprolactinoma was found at computed tomography (of 0.77 by 0.71 cm). Cabergoline was started and progressively increased up to 1.5 mg per weekly. The prolactin quickly normalised up to 8 ng/mL within 4 months. The fertility was allowed after a few months but no couple fertility tests were further taken by the family. She was followed for 2 years and the imagery found a tumour reduction to 0.44 by 0.42 cm with normal prolactin levels. (Figure 2)

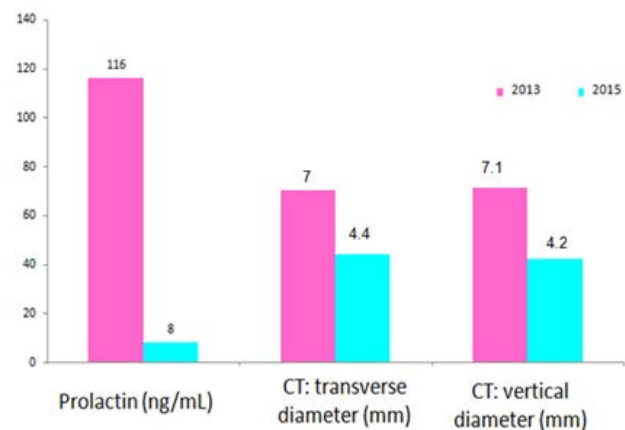


Figure2. The prolactin and computed tomography results from baseline (2013) and after 2 years of cabergoline therapy (2015)

Discussions

Several key points are introduced based on these cases. The first case associates the idea of a newly diagnosed microprolactinoma during menopause. Although the main differential diagnosis with a breast disease associated hyperprolactinemia plus a pituitary incidentaloma is difficult to distinguish the persisted high values of prolactin and their normalisation under dopamine analogues is the

main argument for a microprolactinoma. Studies have showed the need to treat prolactin producing tumours including through the menopausal years. [6] The main reason of this is the bone status. It is well known the hyperprolactinemia associated bone loss in pre and post- menopause. [7,8,9] It seems that a direct effect of high prolactin levels on skeleton is presented independent of hypoestrogenic state. [10]

The prolactinoma- osteoporosis association in a patient with history of kidney stone and associating a DXA pattern with the lowest T-score at distal radius increases the suspicion of a multiple endocrine neoplasia syndrome but in our case the repeated tests ruled out this condition. [11,12] Generally the disorder displays the phenotype at younger age and in this situation the genetic tests are unnecessary. [11,12]

The second case displays the idea of GH control in a newly diagnosed case of macroprolactinoma. [13,14,15] The IGF1 (Insulin Growth Hormone 1) is a screening test in every new case of pituitary adenoma (with reference levels adjusted based on patient's age and sex). [13,14,15] Since the levels of IGF1 may vary an oral glucose tolerance test is useful especially in tumours larger than 1 cm diameter since acromegaly displays in 80-90 % of cases a macroadenoma. [13,14,15] Prolactin-GH co-secretion is found in one tenth of acromegaly cases with a phenotype suggesting either prolactinoma or acromegaly. [13,14,15]

The case number 2 and 3 were misdiagnosed as menopause and this emphasize the importance of taking at least a FSH test in order to indicate the pituitary or ovarian origin of secondary amenorrhea. Another topic is the period of time that should be recommended between the diagnosis of prolactinoma, the therapy start and a pregnancy. A few months are enough in case of a microprolactinoma but if the tumour has more than 1 cm maximum diameter the mass effect might associate severe damage especially on visual field so 6 up to 12 months a pregnancy should be avoided in order to obtain adenoma shrinkage. [16,17] In the second case the patient did not want fertility as was in the third case. In this last case the fertility was actually a couple issues but the family was did not perform further investigations. All the three cases we presented have a particular

aspect: the lack of galactorrhea. Despite the fact that this is one of the most frequent symptoms this might be missing and the underling pathogenic link is less known, probably a hypo- estrogenic state. [18,19]

Conclusions

The prolactinomas interfere with menopause by the importance of continuing dopamine agonists including in cases with menopause onset and by the value of hormonal panel in cases with secondary amenorrhea at reproductive age mimicking menopause.

Conflict of interest:

None

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