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HOW DO I DECIDE WHEN TO DISCONTINUE CABERGOLINE THERAPY IN PROLACTINOMAS?

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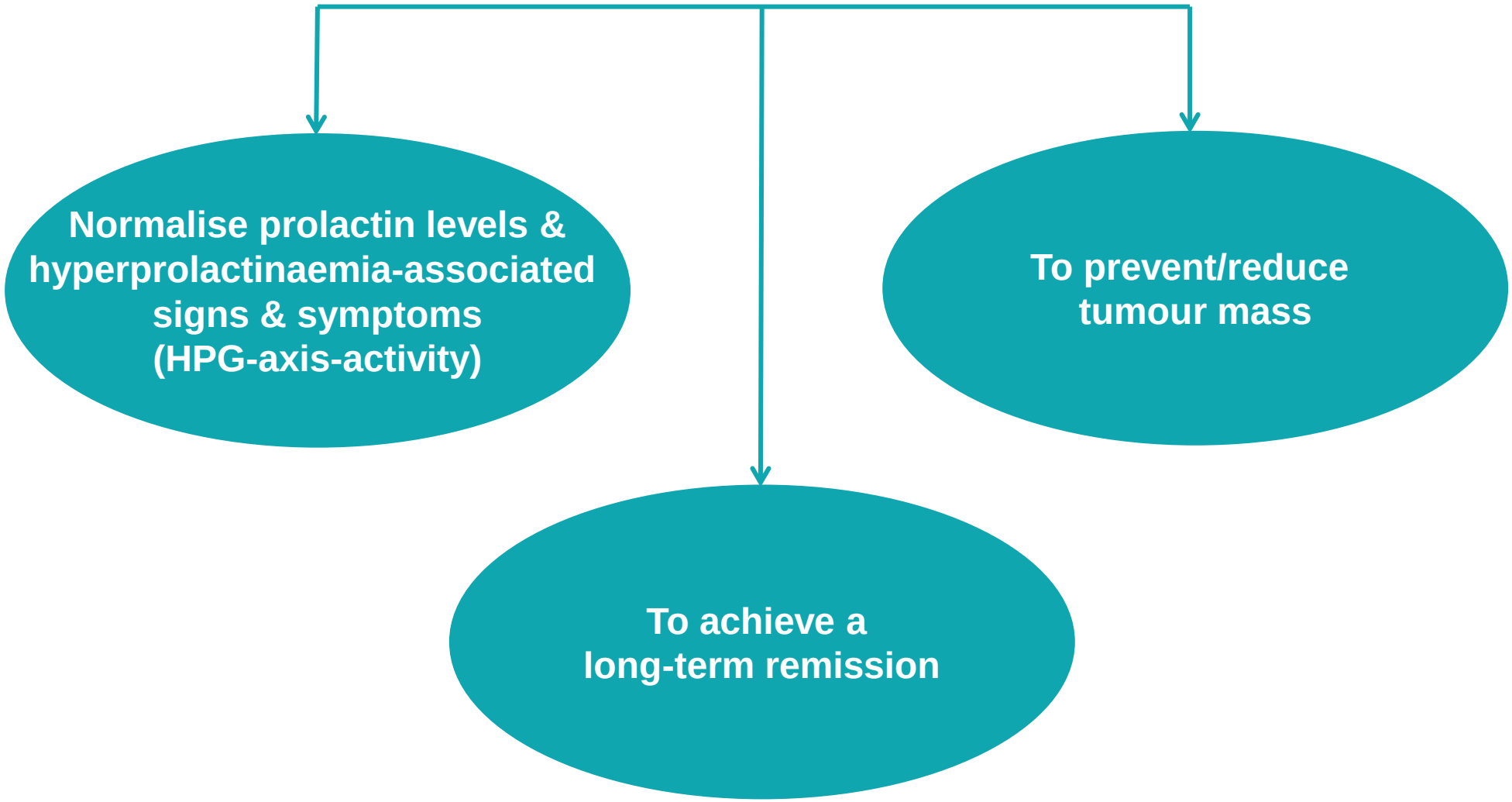
DISCLOSURES

- Dr Vila has no disclosures

AIMS OF THERAPY IN PROLACTINOMAS



HPG, hypothalamic-pituitary-gonadal

Melmed S, et al. J Clin Endocrinol Metab. 2011;96(2):273-88

WHEN DO I STOP CABERGOLINE?

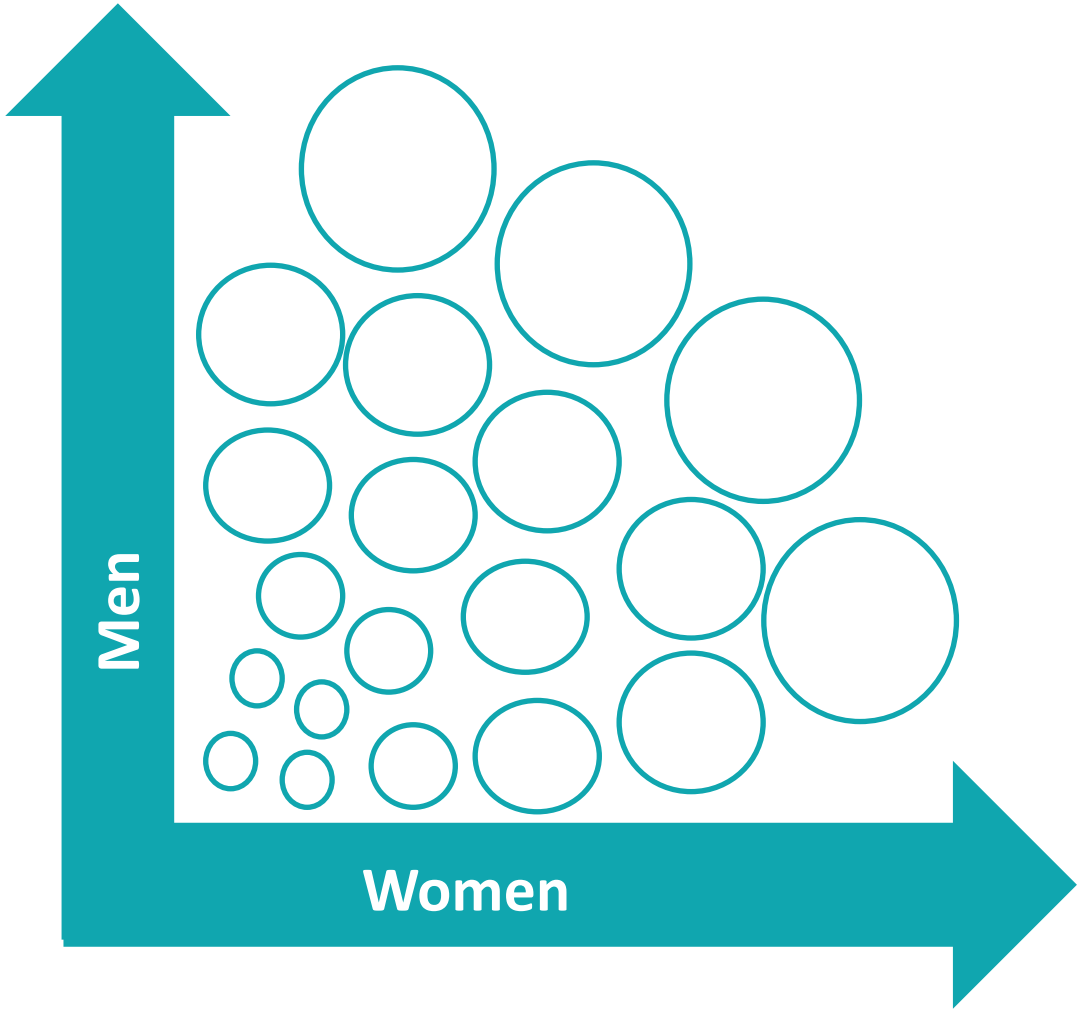
Recommendation

4.3. We suggest that with careful clinical and biochemical follow-up, therapy may be tapered and perhaps discontinued in patients who have been treated with dopamineagonists for at least 2 year, who no longer have elevated serum prolactin, and who have no visible tumour remnant on MRI (2|⊕⊙⊙⊙).

- DA withdrawal may be undertaken in patients who have achieved normoprolactinaemia and significant tumour reduction
- The risk of recurrence after withdrawal is 26-69%
- Recurrence is predicted by prolactin levels at diagnosis and by tumour size (risk of recurrence 18% per mm of tumour mass)
- Withdrawal of therapy is not associated with tumour growth, but 28% of patients may develop hypogonadism

2|⊕⊙⊙⊙ denotes a weak recommendation and very low quality evidence
DA, dopamine agonist; MRI, magnetic resonance imaging
Melmed, et al. J Clin Endocrinol Metab. 2011;96(2):273-88

WHEN DO I STOP CABERGOLINE?



Multifactorial decision based on:

1) patient's age and sex
2) fertility issues
3) adenoma size
4) side effects of cabergoline

HOW TO STOP CABERGOLINE

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ABRUPTLY: immediate stop at any dose

1. **When cabergoline is not needed any more**
   - pregnancy in a female with microprolactinoma
   - decision for pituitary surgery (e.g. cabergoline side effects in endosellar microprolactinoma)

2. **Severe side effects**

3. **Lack of efficacy**
   - e.g. tumour progression in aggressive pituitary adenomas, need to switch to temozolomide

HOW TO STOP CABERGOLINE

SLOWLY: gradually reducing the dose over months/years

1. **When treatment targets are achieved**
   - normal HPG-activity, normal prolactin, non-visible tumour
   - prolactin levels below the normal range
   - post-menopausally, normal prolactin, non-visible tumour

2. **In the presence of mild side-effects**
   - e.g. nausea/dizziness/headaches normal HPG-activity, normal prolactin, non-visible tumour

HPG, hypothalamic-pituitary-gonadal

CLINICAL CASES

IMMEDIATE STOP OF CABERGOLINE

CASE 1

PREGNANCY IN A PATIENT WITH MICROPROLACTINOMA

- 25 year-old female, seconda
- Start cabergoline 0.5 mg (2
- Restoration of gonadal func
- Prolactin 35 ng/ml at 6 mor
  0.25 mg weekly
- Patient gets pregnant after
- Had already been advised to
- Normal pregnancy & delivery, no breastfeeding
- In remission one year after delivery: normal prolactin, normal MRI

Prolactinomas

R.5.1. We recommend treating women with a prolactinoma, who are actively seeking pregnancy, with a dopamine agonist and strive for normalisation of prolactin concentrations and restoration of regular ovulatory cycles (⊕⊕⊕◯).

R.5.3. We recommend cabergoline as medical treatment at the lowest possible effective dose until pregnancy is confirmed (⊕⊕◯◯).

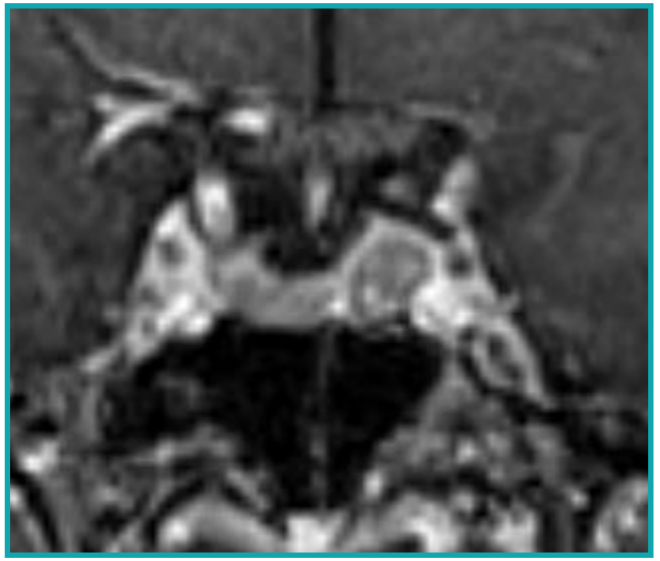
R.5.4. We recommend stopping the dopamine agonist once pregnancy is established. However, dopamine agonists may be given for a longer gestational period in specific circumstances (⊕◯◯◯).

The quality of the evidence behind the recommendations is classified as very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), or strong (⊕⊕⊕⊕)
MRI, magnetic resonance imaging; Tb, tablet
Luger A, et al. Eur J Endocrinol. 2021;185(3):G1-33

CASE 2

DECISION FOR PITUITARY SURGERY

- 35 year-old female, microprolactinoma
- Already on and off cabergoline over 3 years before attending our outpatient clinic
- At the first consultation in our centre, she insists on receiving pituitary surgery, as family planning already delayed
- Gets pregnant one month after successful surgery
- Already had three pregnancies in the last 6 years
- During the 1st pregnancy partial DI, which resolves postpartum
- No other pituitary deficiencies
- In remission: normal prolactin concentrations, normal MRI



DI, diabetes insipidus; MRI, magnetic resonance imaging

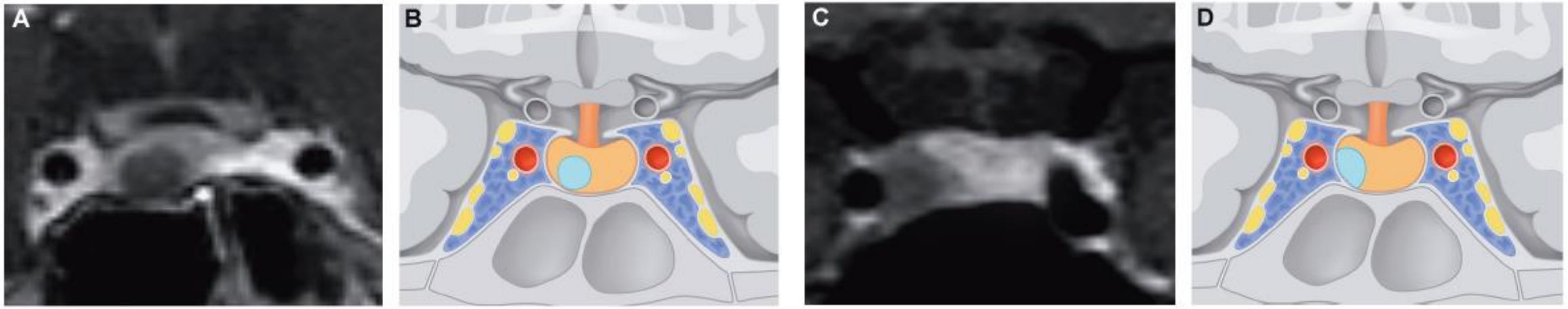
CASE 3

CABERGOLINE SIDE EFFECTS

- 21 year-old female, attends our clinic for a 2nd opinion, currently no partner, does not wish to get pregnant
- Dysmenorrhoea, galactorrhoea, prolactin 89 ng/ml, MRI: 3 mm adenoma
- Severe palpitations on cabergoline (2x1 Tb/week), drowsiness on quinagolide, therapy stopped
- 10 months later: MRI: 5-6 mm adenoma, secondary amenorrhoea
- Had been advised to restart low-dose cabergoline; palpitations, headache
- Neurosurgical evaluation in our centre: endosellar adenoma, surgery planned, 85% remission rate

MRI, magnetic resonance imaging; Tb, tablet

ENDOSCOPIC TRANSSPHENOIDAL SURGERY OF MICROPROLACTINOMAS: CURE RATE BASED ON RADIOLOGIC CRITERIA



Postoperative results

	Group ENC			Group LAT			
	Mean (range)	Median (IQR)	%	Mean (range)	Median (IQR)	%	P
Number of patients	31		52	29		48	NS
Follow-up (year)	27 (0.3-7.3)	1.9 (0.6-4.3)		3.5 (0.3-11.9)	2.5 (1.2-5)		NS
Remission	27		87	13		45	.01
PRL 1st day postoperative	9 (0.3-82)	5.1 (1.4-8)		15 (0.6-61)	7.4 (4.9-22.6)		NS
PRL last control	16 (0.3-148)	10.9 (6-14.8)		38 (0.6-214)	31 (8.1-57.1)		.02
MIB-1 (%)	4.8 (0-25.2)	2.8 (1.6-7.6)		4.1 (0-15.8)	3 (1.2-5.8)		NS

ENC, adenoma enclosed by pituitary gland tissue; IQR, interquartile range; LAT, adenoma located lateral to the gland adherent to the medial cavernous sinus wall; MIB-1, marker of proliferation; NS, nonsignificant; PRL, prolactin

Micko A, et al. Neurosurgery. 2019;85(4):508-15

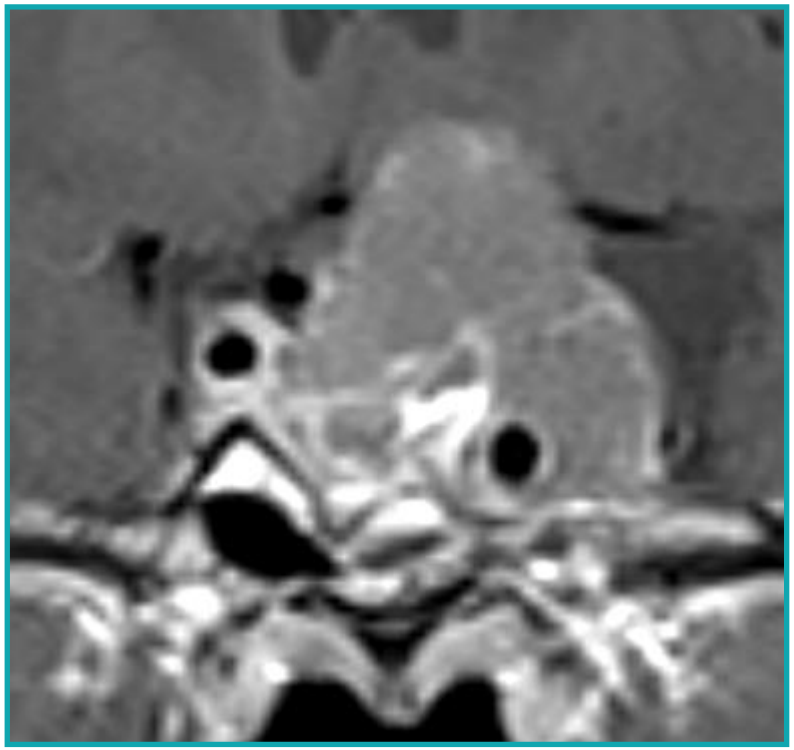
CLINICAL CASES

SLOW BUT CONTINUOUS DOSE REDUCTION

CASE 4

59 YEAR-OLD MALE, MACROPROLACTINOMA

- Macroprolactinoma diagnosed 22 years ago
- Since then cabergoline therapy, dose gradually reduced during the last years
- Prolactin 3.4 ng/ml, under 0.5 mg cabergoline weekly
- No visible adenoma on MRI: radiologist describes st.p. pituitary surgery ☺
- Reduction of cabergoline to 0.5 mg and 0.25 mg weekly on alternate weeks
- Re-evaluation after 6 months, and further reduction to 0.25 mg weekly



MRI, magnetic resonance imaging; st.p., status post.

NO MRI FOLLOW-UP NEEDED IN PATIENTS WITH MACROPROLACTINOMAS AND LONG-TERM NORMAL PROLACTIN LEVELS ON DA TREATMENT

Characteristics of the patient cohort	
Sex ratio	63 M/52 F
Mean age at diagnostic (years ± SD)	36.3 ± 14.9
Mean initial prolactin (ng/ml)	2,224 ± 6,839
Mean largest diameter at diagnostic (mm ± SD)	21 ± 10.6
Mean age at last follow-up (years ± SD)	48.8 ± 16.1
Mean length of follow-up (years ± SD)	9.7 ± 5.8
Haemorrhagic changes during DA treatment	21 (18.2%)
Empty sella turcica at final elevation	29 (25.2%)

- Repeat MRI follow-up does not prove to be necessary when prolactin concentrations reach the normal range on DA (i.e. sometimes after up to 3 years after their onset) in patients with macroprolactinomas

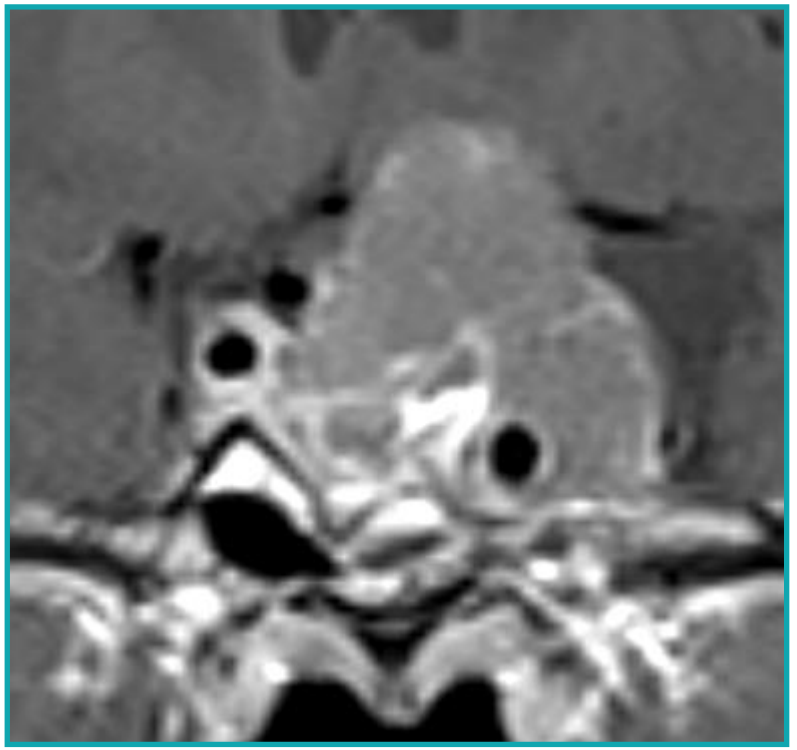
DA, dopamine agonist; F, female; M, male; MRI, magnetic resonance imaging; SD, standard deviation

Eroukhmannoff J, et al. Eur J Endocrinol. 2017;176(3):323-28

CASE 5

35 YEAR-OLD MALE, MACROPROLACTINOMA

- Diagnosis at the age of 18 years, adenoma size 22×18×15 mm
- Cabergoline therapy
- Prolactin 8 ng/ml, cabergoline stopped by urologist at age 34 years
- One year later: prolactin 137 ng/ml, adenoma 12×7 mm
- Start with cabergoline 0.5 mg weekly, normalisation of prolactin within 4 months



TAKE-HOME MESSAGE

- DA withdrawal can be done abruptly in case of pregnancy or DA side effects in microprolactinomas
  - The rate of surgical remission is high in endosellar microprolactinomas (86%)
- High risk of recurrence in young patients with macroprolactinomas, a slow down-titration of cabergoline dose aiming to maintain normal prolactin levels is more efficient and also reduces the need for MRI examinations

DA, dopamine agonist; MRI, magnetic resonance imaging

Micko A, et al. Neurosurgery. 2019;85(4):508-15

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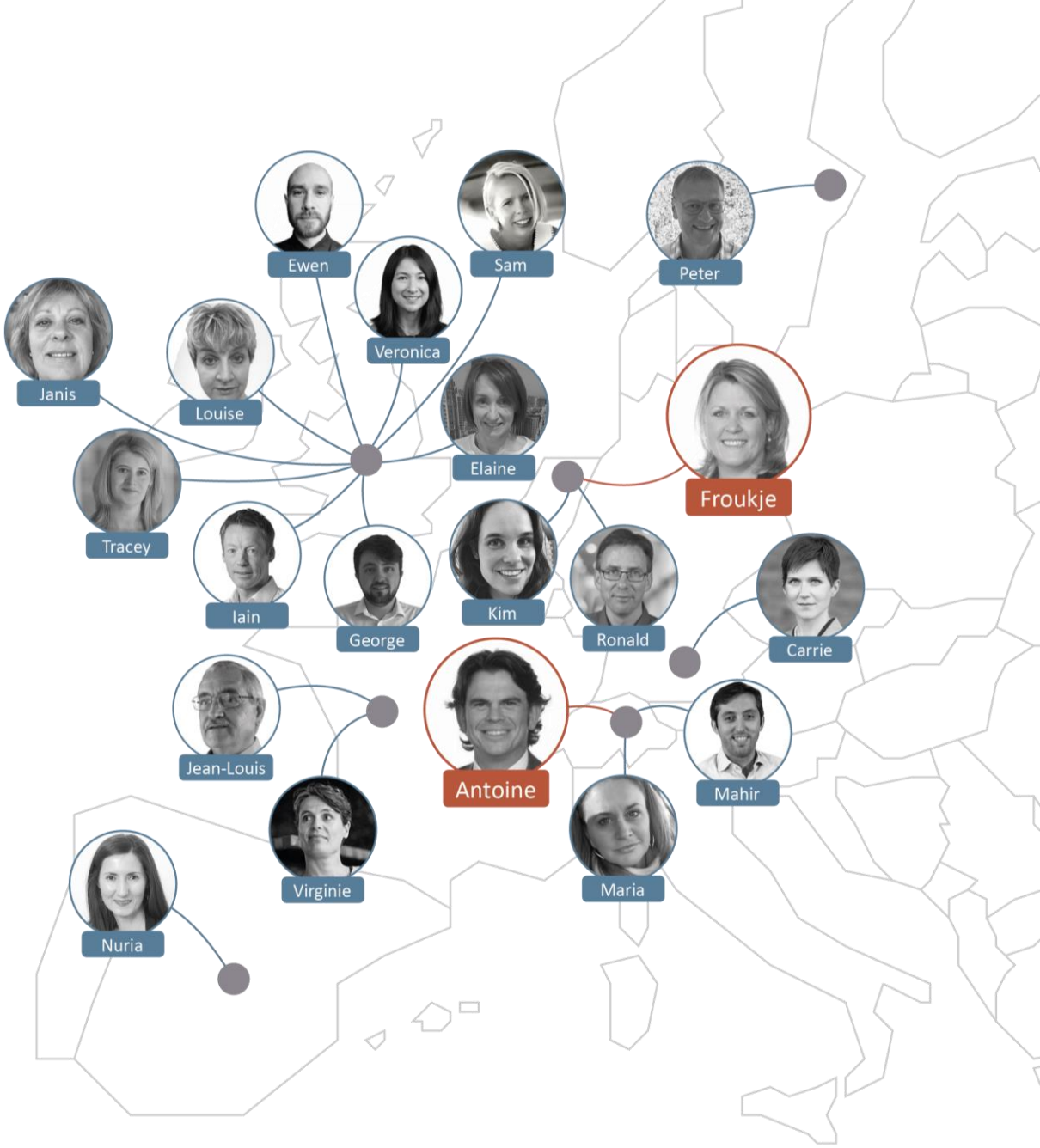

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