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Pasireotide: A potential therapeutic alternative for resistant prolactinoma Pasiréotide, une alternative thérapeutique pour les prolactinomes résistants ?

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1

2 **Abstract**

3 **Context:** About 10% of prolactinomas are resistant to dopamine agonists (DAs). The
4 only alternatives for tumor and prolactin control are surgery or radiotherapy. While
5 studies on first-generation somatostatin analogs have shown no efficacy against
6 prolactinomas, no study has been conducted on the new multireceptor-targeted
7 somatostatin receptor ligand pasireotide, which presents high affinity for 5, 3, 2 and
8 1 receptor subtypes.

9 **Case description:** A 41 year-old woman presented with a macroprolactinoma
10 showing resistance to all available DAs. She was first diagnosed at 17 years old after
11 which she had undergone two incomplete debulking surgeries. Under pasireotide
12 long-acting release (LAR) treatment, plasma prolactin levels normalized and
13 symptoms disappeared within one month after initiation. The clinical benefits of the
14 monotherapy (specifically, prolactin levels within normal range and stable tumor
15 volume) were maintained for seven years. Glucose tolerance was satisfactory.
16 Pathological analysis of the tumor revealed high SSTR5 and low SSTR2 expression
17 (25 and 5% of cells respectively).

18 **Conclusion:** This is a promising first report of a patient with a DA-resistant
19 macroprolactinoma who achieved long-term control, in terms of prolactin
20 normalization and tumor volume, under pasireotide treatment alone. Pasireotide
21 could thus be an alternative in prolactinomas resistant to DA. SSTR expression
22 analysis on pathology could guide patient selection.

23

24 **Keywords:** Pituitary tumor, prolactinoma, aggressive tumor, somatostatin receptor,
25 pasireotide

26

27 **Résumé**

28 **Contexte :** Dix pour cent des prolactinomes sont résistants aux agonistes
29 dopaminergiques (DAs), offrant comme seules possibilités thérapeutiques, pour
30 contrôler la tumeur et la prolactinémie, la chirurgie ou la radiothérapie. Alors que les
31 analogues de la somatostatine de première génération n'ont pas montré d'efficacité,
32 aucune publication ne rapporte l'effet du pasiréotide, analogue de la somatostatine
33 de nouvelle génération présentant un profil d'affinités plus large, notamment pour les
34 récepteurs des sous-types 5, 3, 2 et 1.

35 **Description :** Une patiente âgée de 41 ans a été adressée pour un
36 macroprolactinome évoluant depuis l'âge de 17 ans, résistant aux agonistes
37 dopaminergiques, ayant nécessité deux chirurgies d'exérèse incomplète. Après
38 introduction de pasiréotide longue durée d'action (LAR), la prolactinémie s'est
39 normalisée en 1 mois, permettant une disparition des symptômes. L'effet
40 thérapeutique était maintenu au dernier suivi, 7 ans après l'introduction, avec une
41 stabilisation du volume tumoral et une prolactinémie normale. La tolérance glucidique
42 était correcte. L'analyse histologique de la tumeur a retrouvé une forte expression de
43 SSTR5 associée à une faible expression de SSTR2 (25 et 5 % des cellules
44 respectivement).

45 **Conclusion :** Nous rapportons le premier cas de macroprolactinome résistant aux
46 agonistes dopaminergiques, pour lequel un traitement par pasiréotide seul a permis
47 un contrôle de la prolactinémie et du volume tumoral sur le long terme. Ainsi, le
48 pasiréotide pourrait être une alternative thérapeutique dans les prolactinomes

49 résistant aux agonistes dopaminergiques. L'analyse histologique de l'expression de
50 SSTR pourrait aider à sélectionner les patients.

51

52 **Mots-clés** : Tumeur hypophysaire, prolactinome, tumeur agressive, récepteurs à la
53 somatostatine, pasiréotide

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57

58 **Introduction**

59 Prolactinomas are the most frequently encountered pituitary tumor, representing
60 around 50% of all pituitary tumors. Dopamine-agonist (DA) therapy, especially cabergoline,
61 is the first-line treatment and is able to normalize prolactin levels and tumor volume in most
62 cases. However, prolactin levels cannot be normalized by conventional doses in around 10%
63 of prolactinomas [1]. These are considered as DA-“resistant” and present more often as
64 invasive macroadenomas [2]. A tumor size reduction less than 50% maximal diameter is more
65 rarely used as a criterion of resistance. In cases of resistance, or more rarely of intolerance to
66 dopamine-agonists, alternative treatments are surgery and radiotherapy. However, they may
67 not be indicated, depending on the size, localization and firmness of the tumor. Moreover,
68 surgical excision is not always curative, especially in case of invasive tumors, while
69 radiotherapy exposes to side effects such as hypopituitarism.

70 The new multireceptor-targeted somatostatin transmembrane receptor (SSTR) ligand
71 pasireotide is marketed for patients with acromegaly or Cushing’s disease. It can bind to G-
72 protein coupled SSTRs of normal or neoplastic pituitary cells and inhibits hormone secretion
73 and cell growth. Unlike first generation somatostatin analogs (lanreotide or octreotide) which
74 bind preferentially SSTR2, pasireotide binds to multiple SSTRs with a high affinity for
75 SSTR5 followed by SSTR2, SSTR3, and SSTR1[3].

76 We report here the first patient with a DA-resistant macroprolactinoma to present
77 long-term prolactin normalization on pasireotide treatment alone.

78

79

80 **Case-report**

81 In 2010, a 41-year-old woman was referred to us for treatment of a DA-resistant
82 macroprolactinoma.

83 She was diagnosed in 1986 with a macroprolactinoma measuring 15 mm and
84 responsible for galactorrhea and amenorrhea. Initial plasma prolactin levels were 116 ng/mL.
85 The pituitary and visual function assessment were normal. Bromocriptine therapy was
86 progressively increased up to 15 mg/day. In the absence of control over plasma prolactin
87 levels, surgical removal of the tumor was decided five years later in 1991. The pathological
88 examination revealed a grade 2b pituitary neuroendocrine tumor (Fig. 1A) with 100% of cells
89 expressing prolactin (Fig.1B), high mitotic count (n=4), and positive P53 expression. Ki67
90 index was not interpretable because of technical issues.

91 After an initial period of post-operative remission, her initial symptoms recurred one
92 year after surgery. At this point, plasma prolactin levels had risen to 94 ng/mL and a CT-scan
93 revealed a macroadenoma measuring 20 mm in the right sellar region. Bromocriptine (25 mg
94 per day) and quinagolide (225 µg per day) separately failed to normalize plasma prolactin
95 levels. A second partial surgery was required in 2003 to treat a third cranial nerve palsy
96 caused by tumor regrowth that had occurred once DA had been stopped. Cabergoline
97 treatment permitted a temporary and incomplete decrease in plasma prolactin levels which
98 allowed a spontaneous pregnancy in 2007. The patient gave birth to a normal girl but
99 menstruation was not restored despite a continued and intensified treatment with cabergoline
100 up to 4.5mg per week. Plasma prolactin levels rose to 127 ng/mL while MRI showed global
101 stability of the large right sellar residue measuring 33 mm. Moreover, this higher dose of
102 cabergoline was badly tolerated inducing asthenia and dizziness. Radiotherapy was then
103 proposed but refused by the patient.

104 Re-examination of the tumor fragment from the first surgery showed expression of
105 SSTR5 in 25% of cells (Fig.1C) whereas only 5% expressed SSTR2 (Fig.1D). The analysis of
106 genes *AIP* and *MEN1* revealed no mutation.

107 As part of a clinical trial (ClinicalTrials.gov Identifier: NCT00958841, approved by
108 ethical committee of Hospices Civils de Lyon), pasireotide LAR was begun in October 2010
109 at 60 mg every 28 days. This normalized plasma prolactin levels within one month (Fig. 2)
110 and allowed the stopping of cabergoline three months later. At this point, amenorrhea-
111 galactorrhea had stopped and MRI revealed a global stability of tumor size with necrotic
112 transformation **suggestive for an anti-tumor effect** (Fig. 2). The treatment was well tolerated
113 without any digestive disorders. There was no diabetes mellitus, but glucose intolerance
114 occurred as shown by HbA1C rising from 5.7% to 6.2% and fasting plasma glucose level
115 from 0.90 to 1.20 g/L then to 1.27 g/L six months after pasireotide initiation. However, this
116 required no pharmacological treatment and the implementation of dietary measures was
117 sufficient.

118 Treatment was progressively decreased to 20 mg every five weeks. At the last follow-up
119 seven years after pasireotide initiation, the plasma prolactin levels were maintained within the
120 normal range and MRI showed a stable residual tumor. Tolerance was correct, fasting plasma
121 glucose was 0.97 g/L and HbA1c was 5.7%.

122

123 **Discussion**

124 We report here the first case of a DA-resistant macroprolactinoma demonstrating a
125 clinical and hormonal response to pasireotide treatment allowing its long-term control.

126 Pasireotide is a new somatostatin receptor ligand currently prescribed in patients with
127 acromegaly, Cushing's disease and neuroendocrine tumors. Compared to lanreotide and
128 octreotide, it has a broader binding profile and significantly higher *in vitro* affinity for SSTR
129 1, 3 and 5 receptors (respectively 30, 5 and 40 times), and a lower one for SSTR 2 receptors
130 (2.5 times) [3].

131 The expression of somatostatin receptor subtypes has already been described in human
132 prolactinomas [4–6] and in light of our results presented here, may justify the potential use of
133 somatostatin analogs in the treatment of prolactinomas. Both immunohistochemistry studies,
134 via use of a scoring system (associating % of immunopositive cells and membrane staining
135 pattern), and mRNA studies have shown the expression of three subtypes of SSTR in human
136 prolactinomas: SSTR1, 2 and 5. The level of expression is highly variable depending on the
137 tumor, but all studies found higher SSTR5 expression followed by lower and variable levels
138 of expression of SSTR2A and SSTR1 [4–6]. The expression pattern has never been associated
139 with DA resistance, tumor size or aggressiveness [5].

140 A role for SSTRs in prolactin secretion is suspected. However, results from *in vitro*
141 studies on use of somatostatin analogs in prolactinomas are inconsistent. In some studies,
142 octreotide significantly reduced prolactin secretion of primary human prolactinoma and mixed
143 growth hormone and prolactin (GH-PRL)-secreting cultured cells [7,8]. Other studies showed
144 an uncertain and modest reduction of prolactin secretion and cell viability, especially using
145 octreotide [6,9,10]. These inconsistencies could be due to differences in SSTR2 expression, as
146 indicated by Acunzo *et al.* who observed prolactinomas becoming sensitive to octreotide only
147 after *SSTR2* gene transfer [10,11]. Evidence suggests that pasireotide may be more effective

148 than other somatostatin analogs at reducing prolactin secretion. In 1999, Jaquet *et al.*
149 demonstrated that another somatostatin agonist (BIM-23268) with high affinity for SSTR 5
150 could inhibit prolactin release from human prolactinomas in primary culture. This 26 to 90%
151 reduction was higher compared to the one induced by octreotide [5]. More recently,
152 pasireotide and octreotide effects on human prolactinoma and GH/PRL-secreting tumor were
153 compared *in vitro*. Pasireotide could reduce PRL secretion between 38 and 74 % in GH/PRL
154 and between 23 and 80% in PRL tumors, compared to the reduction achieved with octreotide
155 of between 16 and 66% in GH/PRL and 0 and 30% in PRL tumors [7]. An *in vivo* study in
156 mouse GH/PRL adenomas then showed not only a greater reduction in prolactin secretion
157 with pasireotide compared to with octreotide but also a superior anti-tumor effect [12].
158 However, the effects of pasireotide did not differ significantly from octreotide in other recent
159 studies [6,8,9]. Moreover, in these latter studies, the effect of somatostatin analogs on
160 prolactin secretion was weaker than that of DAs, even in prolactinomas considered as
161 resistant [5–7].

162 As suggested by *in vitro* studies, the SSTR profile of prolactinomas may explain the
163 mainly disappointing results of first generation somatostatin analogs in treating
164 prolactinomas. Only one successful case of octreotide treatment has been reported [13] in a
165 young man who had previously undergone two surgical excisions. Initiation of octreotide at
166 20 mg every 28 days in association with cabergoline led to normalized plasma prolactin levels
167 at the 12 month follow-up and stability of the pituitary tumor at 2 years, as shown by MRI.
168 All other studies using cyclic synthetic somatostatins or octreotide reported therapeutic
169 failures [14].

170 Clinical effects of the second-generation somatostatin analog pasireotide on
171 prolactinomas have not yet been reported in the literature. Our report demonstrates the
172 efficacy of pasireotide to normalize prolactin secretion, achieve long-term control over tumor

173 volume and restore the menstrual cycle in a woman with a resistant prolactinoma ineffectively
174 treated over the previous 24 years with high doses of all available dopamine agonists
175 (bromocriptine, quinagolide, cabergoline). In such cases of DA-resistant prolactinoma, this
176 treatment could be proposed before considering radiotherapy or temozolomide treatment
177 options.

178 No significant adverse effects of pasireotide were observed in this patient. Digestive disorders
179 and hyperglycemia are usually the most frequent adverse effects of this drug. As pasireotide is
180 associated with a reduction in the secretion of the hormones insulin and incretin,
181 hyperglycemia and diabetes are observed in 30% of acromegalic patients and up to 70% of
182 patients with Cushing' disease. However, the glucose tolerance disturbance induced by the
183 IGF1 and cortisol excess likely potentiates the hyperglycemia occurring under pasireotide. A
184 lower rate of hyperglycemia events should be expected in patients with prolactinoma.

185 In acromegalic patients, the relation between SSTR subtypes expression by
186 immunohistochemistry and response to somatostatin analogs is suggested [15,16]. Our results
187 support this hypothesis in prolactinomas for which SSTR5 expression is significant. SSTR
188 subtype expression profile could therefore potentially guide therapeutic choice and allow a
189 personalized therapy for these rare patients.

190 In conclusion, our case has demonstrated the potential role of pasireotide for treating DA-
191 resistant macroprolactinomas. SSTR expression may guide the choice of therapy. However,
192 pasireotide being quickly efficient, administration as a short therapeutic test may be sufficient
193 to identify potential responders.

194

195

196

197 **Patient consent**

198 The author confirm that informed consent has been obtained from the patient for publication
199 of the case report and accompanying images.

200

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204

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208

209 **Disclosure summary**

210 The authors declare that they have no competing interest.

211

212

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269 1986.
- 270
- 271

272 **Figures legends:**

273 **Figure 1:** Histopathological features of the first surgical specimen (original magnification x
274 400)

275 A- On hematoxylin phloxine saffron staining, the tumor shows a diffuse growth pattern.
276 Anisokaryosis is moderate and numerous nuclei show a prominent nucleolus.

277 B- The majority of neoplastic cells show typical paranuclear prolactin immunoreactivity.

278 C- A moderately intense membranous immunoexpression of SSTR5 is observed in 25% of
279 neoplastic cells.

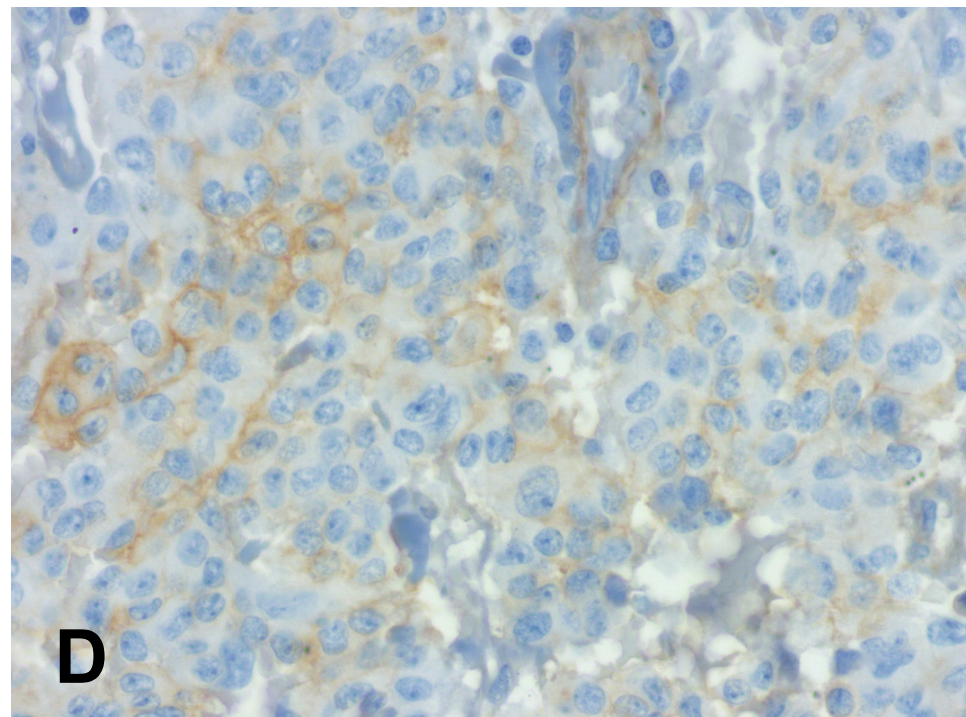
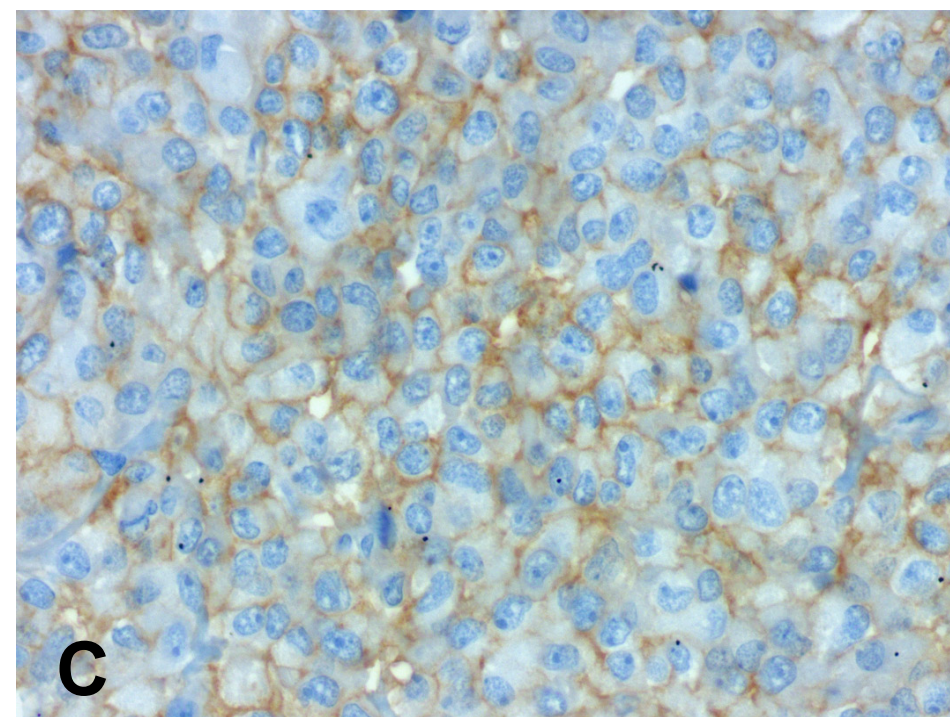
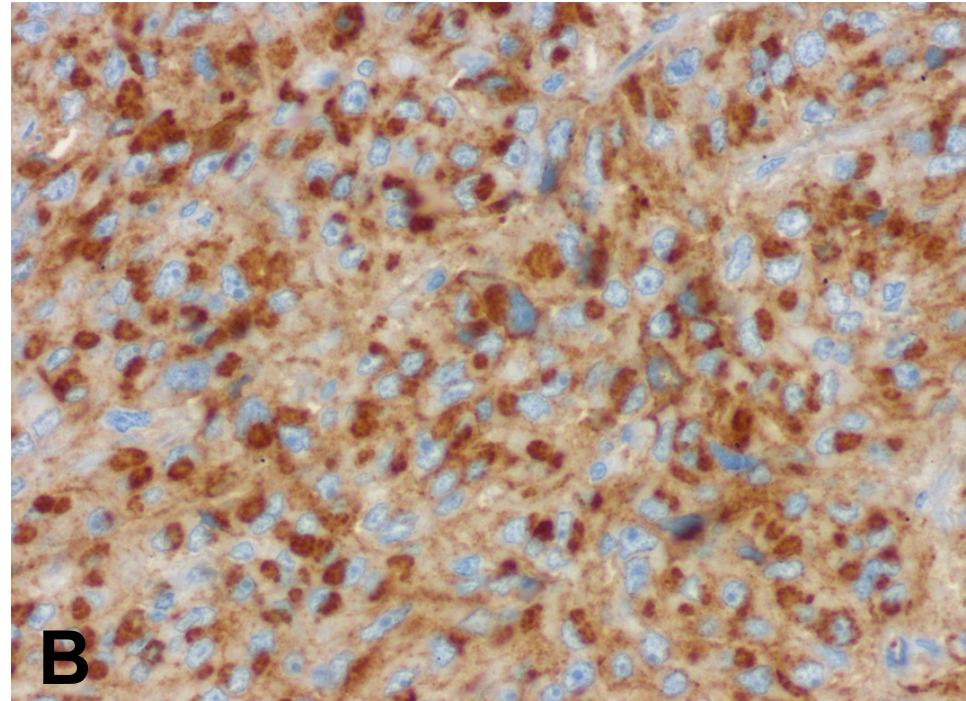
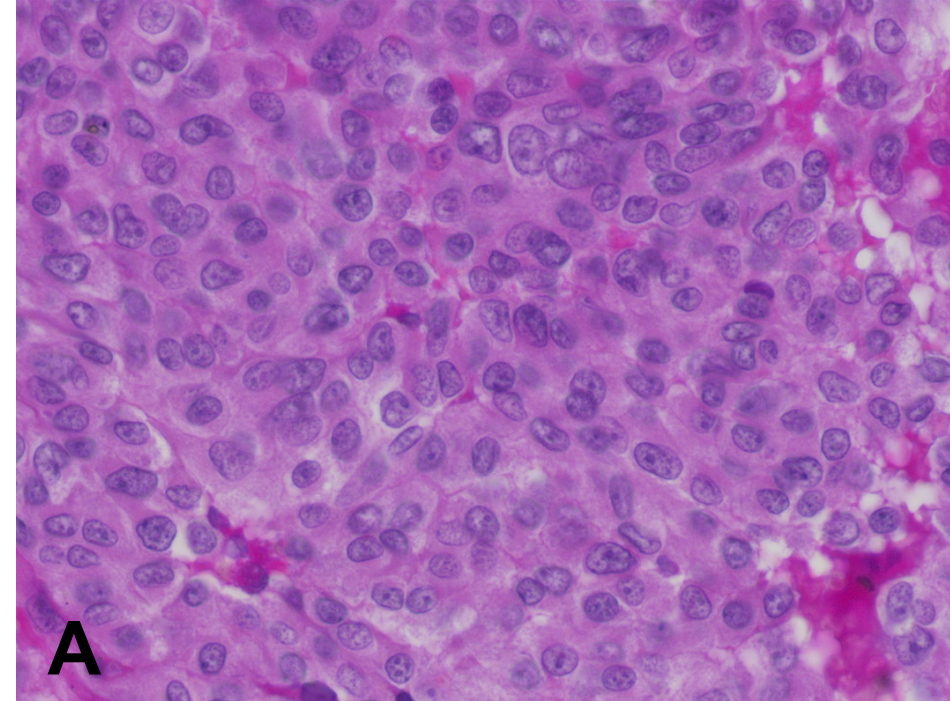
280 D- Only 5% of neoplastic cells show a membranous immunopositivity for SSTR2.

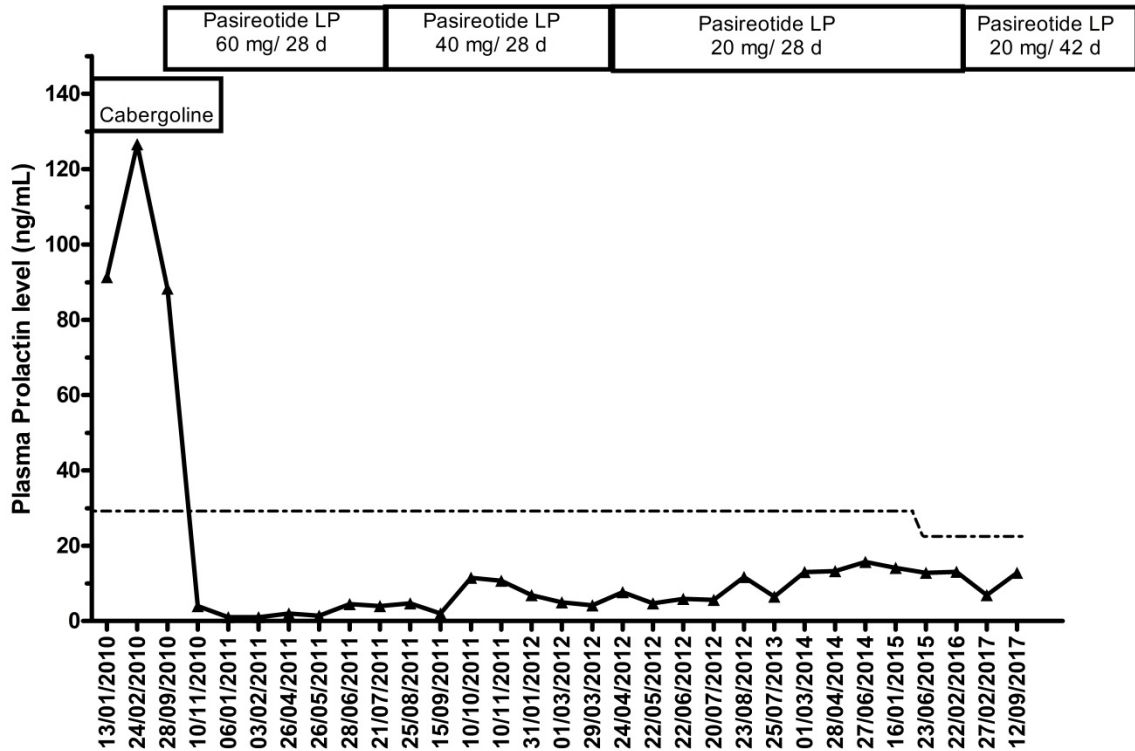
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282 **Figure 2:** Prolactin levels and MRI evolution (four years before pasireotide initiation (2006),
283 at pasireotide initiation (2010-MO), at 3 months after pasireotide initiation (2010-M3) and at
284 the last follow-up (2017)).

285

286





2006

2010-M0

2010-M3

2017

