

STUDY OF THE PULSATILITY OF GONADOTROPHINS AND PROLACTIN IN HYPERPROLACTINAEMIC PATIENTS, WITH OR WITHOUT RADIOLOGICAL EVIDENCE OF PITUITARY ADENOMA

INTRODUCTION

The secretion of prolactin appears to be controlled ⁽¹⁾ by the tonic release on the part of the hypothalamic centres of a prolactin inhibition factor (PIF) which, conveyed along the portal system, reaches the pituitary, where it acts at the level of the cells secreting prolactin, modulating their secretion.

The nature of the PIF and its mechanism of action still remain unclear. It has been discussed, in fact, whether PIF is dopamine itself or a small hypothalamic peptide.

There are various factors capable of increasing the circulating prolactin. In hyperprolactinaemia, with or without galactorrhoea, amenorrhoea is generally present when the PRL values exceed 10-200 ng/ml ⁽²⁾.

Such situations regress if the hyperprolactinaemia is corrected spontaneously, pharmacologically (L-DOPA, 2 Br- α -ergocryptine) ⁽³⁾, surgically ⁽⁴⁾ or radiologically ^(5,6).

What may be the site of the biochemical defect in such situations, either, that is, at hypothalamic-pituitary level or at the level of the gonad itself, has been actively investigated. A concentration of the PRL between 30 and 200 ng/ml is not pathognomonic of a prolactin-secreting tumour, while concentrations of more than 300-500 ng/ml are almost certainly associated with a PRL-secreting pituitary tumour. In patients affected by hyperprolactinaemia, true micro-adenomas that do not produce any deformation of the sella turcica are fairly common, but on the other hand a sella turcica that is definitely enlarged is a relatively infrequent finding among these patients. Pituitary adenomas of considerable dimensions may lead to changes in the visual field or the fundus oculi, but in this case they are observed in patients with a long history of hypogonadism and sterility.

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SUMMARY

The present study considers the pulsatility of gonadotrophins and prolactin in hyperprolactinaemic patients, with or without radiological evidence of pituitary adenoma.

The hyperprolactinaemic patients with radiological changes of the sella turcica presented on the one hand with higher values of prolactin (PRL) and on the other with lowered values of gonadotrophin and both as regards basal tone and pulsatility.

The diagnostic classification of the « functional » patients appears, however, more uncertain.

Within this group it does not seem possible, in fact, to differentiate the true functional forms from those with pituitary micro-adenoma, on the basis of the fundamental or dynamic hormonal data.

The importance of an appropriate radiographic investigation is discussed in this connexion.

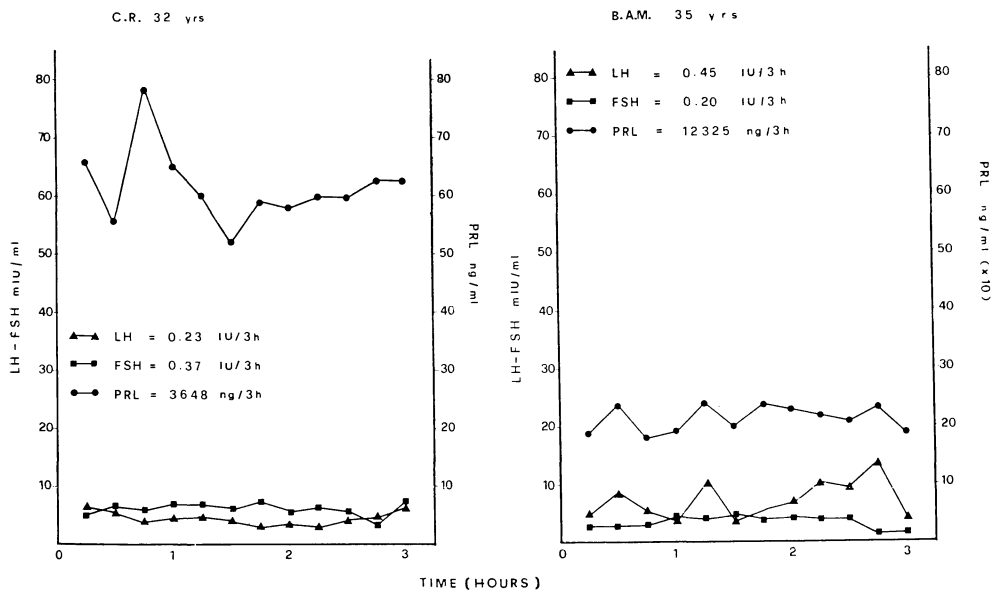


Fig. 1. — Plasma levels of PRL, FSH and LH in two patients (case 1 and 2), without radiological changes of the sella.

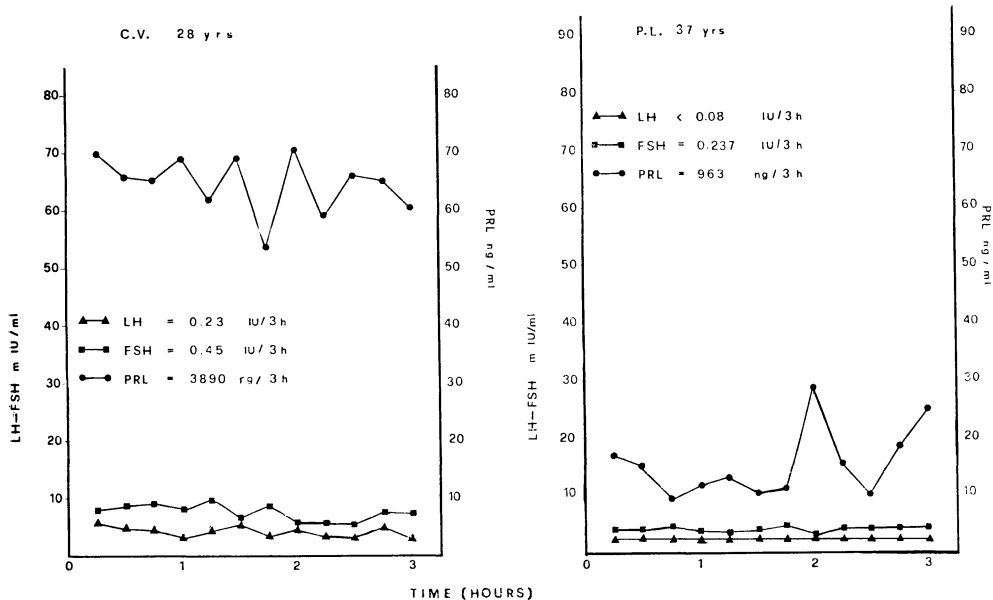


Fig. 2. — Plasma levels of PRL, FSH and LH in two patients (case 3 and 4), without radiological changes of the sella.

Menstrual changes in hyperprolactinaemic patients may or may not be associated with galactorrhoea.

Various checks have been made in order to establish the cause of hyperprolactinaemia, with or without galactorrhoea.

If increased values of PRL are found, even if no pituitary increase can be demonstrated radiologically, it is possible

For PRL, suppression tests with L-DOPA (0.5 g orally), CB-154 (2.5 mg orally) or when loaded with water (20 cc per kg weight), may be used (9).

These tests may provide interesting information, but have not proved as useful as was hoped initially in the differential diagnosis of the organic and functional causes of hyperprolactinaemia, even thou-

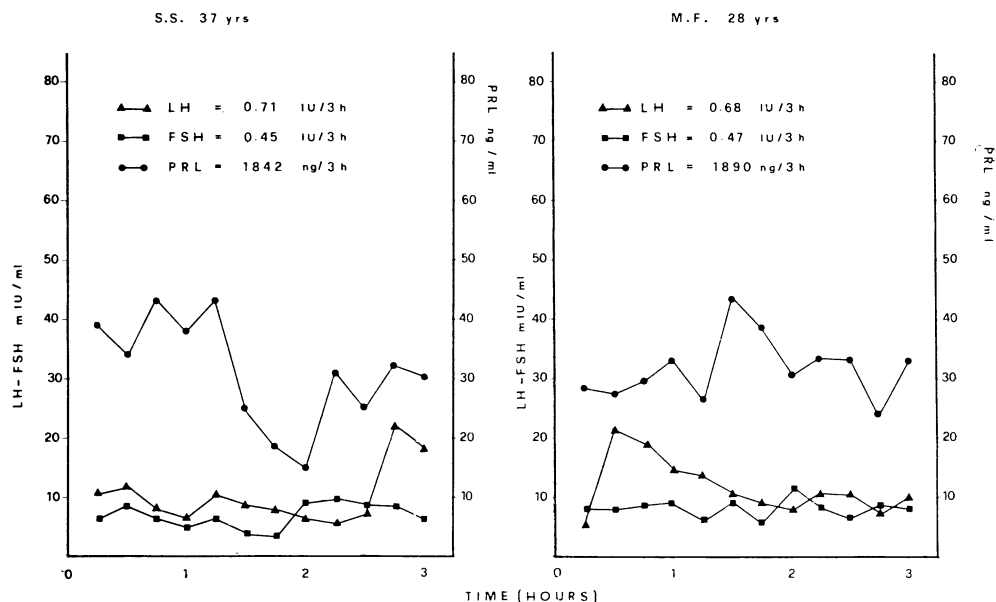


Fig. 3. — Plasma levels of PRL, FSH and LH in two patients (case 5 and 6), without radiological changes of the sella.

and even probable that a certain number of these patients will be suffering from pituitary adenoma.

There are many data in the literature that bear out the slow growth of these tumours over a period of many years.

Whenever a hypothalamic-pituitary lesion is suspected, tests of pituitary function are indicated.

These tests measure PRL, HGH, TSH, LH, FSH, both basally and under specific stimulus (7, 8).

gh, for example, patients with a PRL of more than 200 ng/ml and with no response to TRH are probably carriers of a tumour.

In a recent work of ours (10) we found that high PRL values were present in 15 % of patients affected by secondary amenorrhoea and in 64 % of those affected by amenorrhoea and galactorrhoea.

In the present study we shall consider the values of FSH, LH and PRL in 11 hyperprolactinaemic patients with or without changes in the radiographic picture.

TABLE 1. — *Clinical picture found in hyperprolactinaemic patients without radiological changes demonstrable in the sella turcica.*

Patient	Age (yrs)	Pregnancy	Case history	Menstrual changes (duration in years)	Galactorrhea	Radiological changes (tomography)	Changes in fundus oculi	Changes in visual field	PRL ng/ml max. value
1) C.R.	32	+ (after Pergonal + Profasi)	Tablet	A ₄	+	—	—	—	79
2) B.A.M.	35	—	Psychopharm. tablet + electro-shock	A ₄	+	—	—	—	240
3) C.V.	28	—	Anorexic drugs	O ₂	+	—	—	—	71
4) P.L.	37	—	Extreme fright	A ₁₆	+	—	—	—	29
5) S.S.	37	—	Psychopharm. tablet	O ₁	+	—	—	—	43
6) M.F.	28	—	Tablet	A ₄	+	—	—	—	44
7) C.A.	26	—	Polycystic ovary	A ₃	+	—	—	—	96

A = amenorrhoea.
O = oligomenorrhoea.

TABLE 2. — *Clinical picture found in hyperprolactinaemic patients with radiological changes in the sella turcica.*

Patient	Age (yrs)	Pregnancy	Amenorrhoea for years	Galactorrhea	Radiological changes (tomography)	Changes in Fundus oculi	Changes in visual field	PRL ng/ml max. value
1) P.M.R.	27	—	4	—	enlarged sella	+	+	342
2) F.C.	27	—	9	—	»	—	—	410
3) C.M.P.	35	+	9	+	»	—	—	320
4) V.M.I.	25	—	6	+	»	—	—	280

TABLE 3. — *Integrated values of FSH, LH, PRL in hyperprolactinaemic patients with (+) and without (—) radiological evidence of pituitary adenoma (for explanation see text).*

Patients	LH IU / 3h	FSH IU / 3h	PRL ng / 3h
+	0.20 ± 0.01	0.11 ± 0.03	15740 ± 1535
—	0.36 ± 0.1	0.35 ± 0.04	4170 ± 1417

Mean ± standard error.
For all values P < 0.01.

MATERIAL AND METHODS

Eleven patients were studied. Their clinical data are summarized in tables 1 and 2.

The samples were obtained in the morning at the same hour in order to avoid circadian variations. In order to obtain more comparable samples, a Butterfly no. 19 needle was inserted into a vein of the arm and left in situ with an infusion of physiological solution. This infusion was stopped every 15 min., and after releasing about 2 cc of blood in order to avoid diluting the sample, about 3 cc of blood was collected in heparinized plastic tubes. The samples of heparinized blood were centrifuged after 3 h at 4 °C and the plasma obtained was preserved at —20 °C until required for analysis.

The FSH, LH and PRL were measured during the same assay by the RIA method, using commercially available material (SERONO kits).

The hormonal values are shown with the values for integrated areas related to FSH, LH and PRL, calculated by the method of triangulation and expressed as IU/3 h for FSH and LH and as ng/3h for PRL.

RESULTS

The plasma levels of PRL, FSH and LH that were found in the patients without radiological changes of sella (listed in table 1) are shown in fig. 1-4.

Fig. 5 and 6 show the patterns of prolactin and gonadotrophins of patients with radiological changes of the sella (listed in table 2).

The mean values (± SE) of the integrated areas of the patterns of PRL, FSH and LH found in our patients are summarized in table 3.

It is clear that a more pathological radiological picture is accompanied by higher values of PRL, which suggests the

presence of a PRL-secreting pituitary adenoma.

Considering the gonadotrophin values, it is evident that in the presence of an altered radiological picture of the sella turcica, FSH and LH are diminished both as regards basal tone and pulsatility.

Finally, considering the fact that some of our hyperprolactinaemic patients presented with galactorrhoea while others did not, it seems clear that there is no

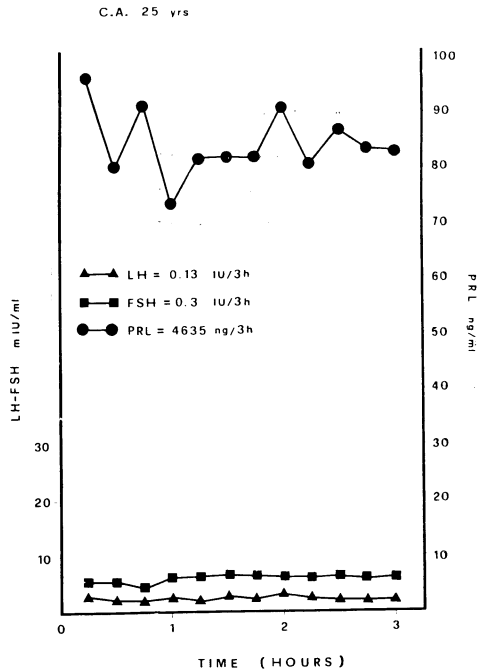


Fig. 4. — Plasma level of PRL, FSH and LH in one patient (case 7), without radiological changes of the sella.

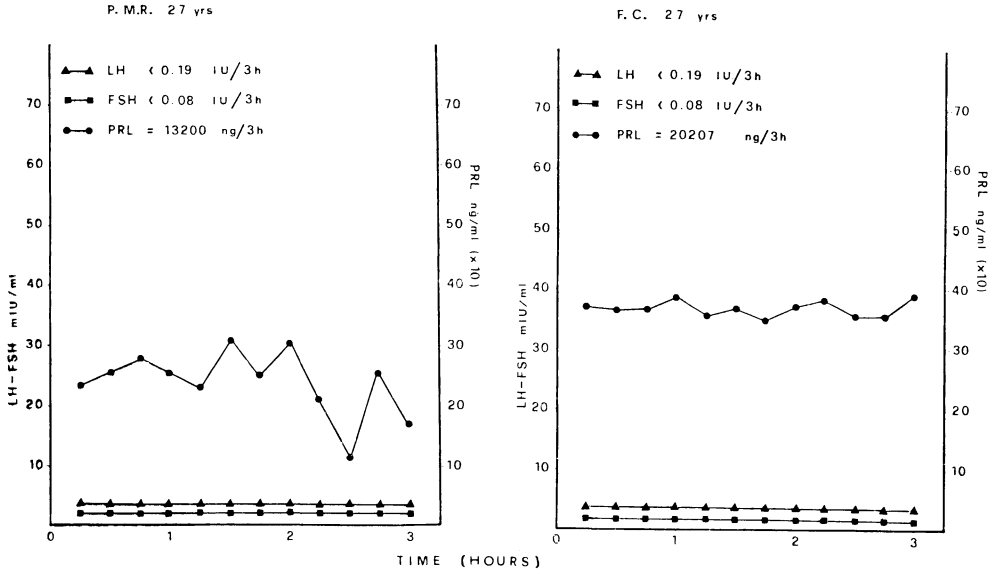


Fig. 5. — Plasma levels of PRL, FSH and LH in two patients (case 1 and 2), with radiological changes of the sella.

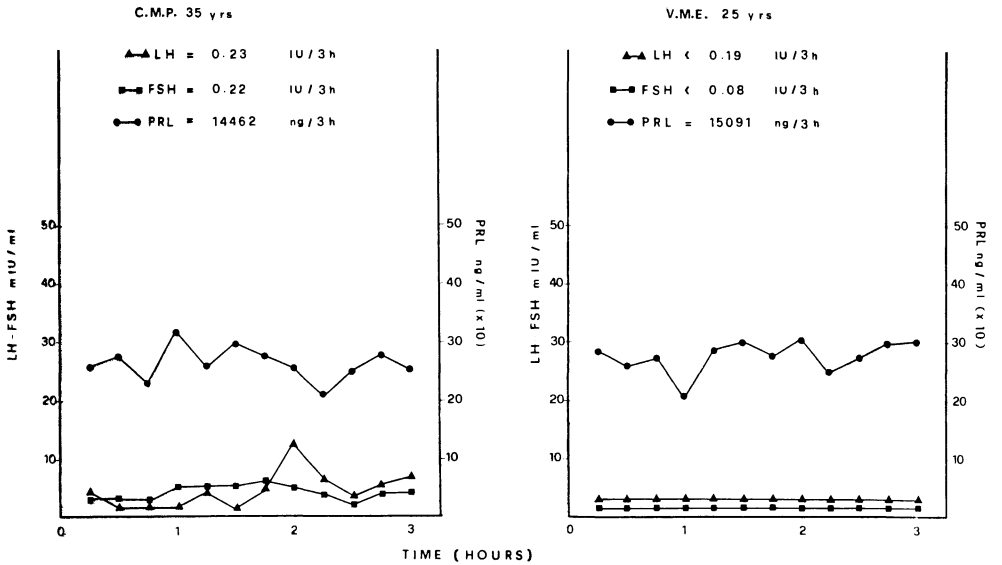


Fig. 6. — Plasma levels of PRL, FSH and LH in two patients (case 3 and 4), with radiological changes of the sella.

need to await the appearance of galactorrhoea before suspecting the presence of a PRL-secreting pituitary adenoma, since clearly there may be cases of pituitary adenomas with hyperprolactinaemia and amenorrhoea but without galactorrhoea. This probably relates to the fact that the secretion of milk, whether it is physiological or pathological, requires a certain hormonal situation and also a certain tissue receptivity of the breast before it can be confirmed.

DISCUSSION AND CONCLUSIONS

It seems clear from our study that hyperprolactinaemic patients with a radiological change in the sella turcica due to the presence of a pituitary adenoma present on the one hand with higher prolactin values and on the other with definitely lower values for gonadotrophins and basal tone and pulsatility.

Considering that the pulsatility of the gonadotrophins is probably related, apart from variations in sensitivity of the gonadotrophin-secreting cells, to variations in the releasing of hypothalamic factors, it may be surmised that the reduced pulsatility of the gonadotrophins corresponds to a reduced synthesis of these factors, or diminished sensitivity of the gonadotrophin cells probably related to hyperprolactinaemia^(11, 12).

This hypothesis is strengthened by the fact that in our patients with radiological alteration of the sella turcica, the GnRH test (100 γ) did not produce any response (data not shown). On the basis of this finding, the determination of gonadotrophins over a period of 3 hours might, in our opinion, replace the GnRH test, at least in these patients with a clear radiological picture of pituitary adenoma. But it is more difficult to deal with the group of patients whom we have attempted to define on the basis of the radiological investigation, as « functional ».

Vezina⁽¹³⁾, studying the sella turcica radiologically, made six sections at intervals of 3 mm in antero-posterior and lateral projection with a hypocycloid movement, and in these circumstances added further stratigrams in the basal projection in order better to evaluate the anterior wall of the sella turcica.

Hypocycloid tomography performed in this way enables the diagnosis of microadenoma to be made if the lesion has increased up to 5 mm (but less than 10 mm).

The number of patients with « functional » hyperprolactinaemia has been markedly diminished by this method, and in many cases the presence of a microadenoma a few millimetres in diameter has been demonstrated; this produces only very slight changes on the lateral border of the sella.

In the light of these considerations, it seems clear that stratigraphic investigation performed in patients with sections made at intervals of 5 mm or more, and mostly in lateral projection, cannot be considered conclusive, it being possible that these patients have a microadenoma.

Within this group, therefore, neither the absolute value of prolactin, nor the pulsatility of the gonadotrophins or of PRL itself, are on the basis of our experience capable of discriminating between the functional form and the microadenoma.

In conclusion, the diagnosis of secreting pituitary adenoma or microadenoma is perhaps a radiological diagnosis in which however an appropriate method has been used.

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