Original Article

Neurological, psychiatric, ophthalmological, and endocrine complications in giant male prolactinomas: An observational study in Algerian population

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ABSTRACT

Introduction: Prolactinomas are less frequent, but more invasive in males. Giant ones (≥4 cm) are extremely rare in literature. Their neurological, psychiatric and endocrine complications are life threatening. Our aim was to report the largest mono center series in order to analyze their frequency, their characteristics, and their complications. **Subjects and Methods:** All patients had clinical examination, hormonal, ophthalmological, and radiological assessment based on computed tomography scan and cerebral magnetic resonance imaging. Positive diagnosis was based on clinical symptoms, high prolactin ± immunohistochemy study. Mixed adenomas were excluded by hormonal exploration and immunohistochemy. For those who received medical treatment only, a reduction in tumor size was considered a supplementary positive point for the diagnosis. **Results:** Among 154 male prolactinomas seen between 1987 and 2013, we observed 44 giant tumors (28.5%). Median age = 36 years, and 38.3% were under 30. Median tumor height = 53.95 mm (40–130) and median prolactin = 15,715 ng/ml ($n < 20$). Solid and cystic aspect ± calcifications was observed in 25%. 42 had cavernous sinuses invasion. Other invasions were: Posterior= 65.9%, anterior= 63.6%, temporal= 15.9% and frontal = 9%. For endocrine complications: Hypogonadism = 98.4%, thyrotroph and corticotroph deficits were seen in respectively 34%, and 32%. Posterior pituitary insufficiency was observed in one case. For ophthalmological complications: Optic atrophy = 46%, Ptosis = 6.8%, diplopia/strabismus = 4.5%. Neurological complications were: Memory loss and/or unconsciousness = 18.2%, epilepsy = 15.9%, frontal syndrome = 9% and obstructive hydrocephalus = 6.8%. **Conclusion:** Giant prolactinomas account for 28% in our population. Severe neurological complications are frequent. But, obstructive hydrocephalus is rare, which argues for a slow progression.

Key words: Giant prolactinomas, male, neurological life threatening complications, optic atrophy, pituitary insufficiency

Introduction

Pituitary tumors secreting prolactin (PRL), also called prolactinomas, are the most common noncancerous pituitary tumors followed by somatotropinomas (tumors secreting growth hormone (GH)) and corticotropinomas (tumors secreting corticotropin hormone or adrenocorticotropic hormone (ACTH)). They usually account for 30–40% of all pituitary tumors[1] although their incidence in autopsy series is greater than 50%.[2] Prolactinomas in general are more frequent in females; but they are larger, more invasive, and more aggressive in men.[3-7]

Giant ones are defined as tumors whose greater diameter is superior or equal to 4 cm with significant extra sellar extension, very high prolactin concentrations, and no concomitant GH or ACTH secretion.[8] They are deemed to be exceedingly rare: 2–3% of all prolactinomas[9] and 0.5% among 2000 pituitary tumors observed by Shrivastava *et al.*[10] Their female to male sex-ratio is equal to 1/9.[11] They are challenging tumors[8] because of their severe ophthalmological consequences and life

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threatening neurological complications. As in literature reported series are very small varying between 4 and 14 cases,[10,12-16] we aimed to report the largest mono centre study in order to analyze their frequency in our population, their clinical and radiological characteristics and their neurological, ophthalmological, and endocrinological complications. This series seems worth to be reported as, apart from the consistent number, the recruitment was conducted in a department of Endocrinology and Metabolic diseases dealing with adults and pediatric endocrinopathies.

Subjects and Methods

154 males harboring prolactinomas seen in our department between January 1987 and December 2013 were analyzed to seek giant ones. In this study we took into account their medical history, clinical examination, hormonal profile, ophthalmological disorders, and radiological aspect. Hormonal assessment was done through radioimmunoassays before 2000 and through chemiluminescence from 2000 till now. Hormonal exploration was based on prolactin (PRL), follicle stimulating hormone, luteinizing hormone, total testosterone (Testo), GH ± insulin growth factor 1, thyrotropin (thyroid-stimulating hormone), free thyroxin (FT4), cortisol, and corticotropin (ACTH). Posterior pituitary function was assessed by 24 h diuresis and urine specific gravity. For ophthalmological evaluation they had visual field, visual acuity, and fundus. Radiological assessment was based on cerebral computed tomography scan and magnetic resonance imaging.

The positive diagnosis was based on clinical presentation (headaches, visual troubles, erectile dysfunction, ± gynecomastia with or without galactorrhea), radiological findings (i.e. pituitary tumor), high prolactin concentrations (levels greater than 200 ng/ml were calculated after appropriate serum dilutions) and immuno-histochemical study (for those who were operated on). Patients with clinical and hormonal values pleading for GH or hypercortisolism secretion were systematically excluded. Hence positive response to dopamine agonists was also taken into account, tumors resistant to dopamine agonist were operated on in order to exclude false prolactinomas (other pituitary tumors with pituitary stalk compression such as nonfunctioning ones, gonadotroph tumors and silent secreting tumors such as somatotropinomas, corticotropinomas, and thyrotropinomas).

Results

Among 154 pituitary tumors that met criteria for prolactinomas, we observed 44 giant ones = 28.5%. Median age at diagnosis was 36 (15–68). Among this group 38.3% were under 30 years old. Median prolactin concentration was 15,715 ng/ml (normal value for our laboratory is ≤ 20 ng/ml) and median tumor height was 53.95 (40–130) mm.

The consultation motive was as follows: Table 1.

Clinical, neurological and ophthalmological examinations and/or explorations revealed the following abnormalities [Table 2].

For radiological aspect, the tumor looks like a craniopharyngioma (solid, cystic ± calcified) in 11 cases (25%). Cavernous sinuses invasion was observed in 42 cases (95.5%). Most of them had cerebral invasion (posterior = 29, anterior = 28, frontal = 4, and temporal = 7).

Table 1: The consultation motive of the 44 patients harboring giant prolactinomas

Consultation motive	Number/44	Percentages
Ophthalmological disorders	22	50
Severe decrease in visual acuity	20	
Bilateral exophtalmos	1	
Diplopia	1	
Severe neurological disorders	16	36.3
Convulsions	07	
Meningitis	04	
Memory loss	02	
Frontal syndrome	01	
Hemiparesis	01	
Dizziness	01	
Other symptoms	05	11.3
Epistaxis	02	
Lack of pubertal development	02	
Severe anemia	01	
Incidental discovery	01	2.4

Table 2: Clinical, neurological and ophthalmological manifestations

Endocrinological, neurological and ophthalmological examinations/ explorations	Number/44	Percentages
Gynecomastia	26	59.1
Galactorrhea	23	52.3
Pituitary insufficiency (≥2 axes)	19	43.18
Obesity	07	15.9
Diabetes insipidus	01	2.2
Severe neurological complications	22	50
Memory loss and/or unconsciousness	08	
Epilepsy	07	
Frontal syndrome	04	
Manifestations of obstructive hydrocephalus	03	
Ophthalmological abormalities	25	56.8
Uni or bilateral optic atrophia	20	
Ptosis	03	
Exophthalmos with or without diplopia and strabismus	02	

Our cases are apparently all sporadic as we did not find any case with a family history of pituitary tumors, and clinical research for multiple endocrine neoplasias (MENs) syndrome was negative.

Concerning the follow-up, except for two cases, all had a significant reduction (more than 50%) in their tumor height and a normalization of their prolactin. For the two cases which were considered as partially sensitive to dopamine agonist, we observed a reduction in their tumor size but their prolactin failed to be normalized, probably because of bromocriptine irregular intake. We did not observe any clinical or radiological manifestation pleading for a malignant tumor.

Discussion

Prolactinomas are the most common benign pituitary adenomas followed respectively by somatotroph, corticotroph, and nonfunctioning tumors.[17] Apart from their mass effect on pituitary function, they produce prolactin whose high plasma and intra gonadal concentrations are responsible for hypogonadism and pathological lactation or galactorrhea. Their clinical manifestations are infertility, menstrual disorders and galactorrhea in women, delayed puberty with or without short stature in children, and central hypogonadism responsible for decreased libido, infertility, erectile dysfunction and gynecomastia with or without galactorrhea in men.[18,19]

Prolactinomas are more frequent in females within the reproductive age than in males, although giant and aggressive ones prevail in males. But, apart from single and anecdotic cases,[20-27] reported series concerning giant prolactinomas in men are scarce and did not exceed 14 cases, probably because of the rarity of giant pituitary tumors in general.

This study showed that in our department, giant prolactinomas account for 28.5% among male population harboring pituitary tumors secreting prolactin. This percentage is very high compared to what was reported in literature. This is probably due to the late diagnosis in emerging countries and to a biased recruitment as our department is considered as a referent one for pituitary tumors.

As observed by others, giant prolactinomas are seen in young population; actually nearly 40% of our patients are under 30 at diagnosis. Our population is younger than Shimon and Corsello's and their median prolactin and tumor heights are greater than Shimon's too.[15]

Giant prolactinomas may be sporadic or be a part of family syndromes such as family isolated pituitary adenomas and MENs. In our population clinical research for MENs syndromes was negative, but genetic testing could not be done for both anomalies, except for some recent cases which are negative.

The giant tumors we observed looked like craniopharyngiomas (solid, cystic ± calcified) in 25%, but posterior pituitary function was deficient in only one case. In agreement with many authors,[28-34] we noted that bone destruction of the surrounding structures mimicking skull base tumors was relatively common. But, as total disappearance of giant prolactinomas takes years, it was difficult for us to know if those pituitary tumors destroying the skull base were eutopic ones or ectopic rising from the clivus.[34] The frequency of cavernous sinuses invasion observed in our series was greater than Shrivastava *et al*.'s.[10] Most of our giant prolactinomas had cerebral invasion which explained neurological and life threatening complications. In our experience the last ones were lacking in prolactinomas measuring less than 4cm in their maximal diameter. Actually an unpublished study done in 2009 in our department comparing 20 giant prolactinomas to 20 prolactinomas measuring less than 40 mm showed that giant tumors secreting prolactin did not differ significantly from smaller ones regarding: Age at diagnosis, prolactin concentration, sexual dysfunction, multiple pituitary deficits, reduction in visual acuity, and radiological aspect. But, as expected cerebral invasion was observed only in giant tumors which could explain the high frequency of memory troubles and life threatening neurological complications such as epilepsy, meningitis and obstructive hydrocephalus.[35]

In agreement with many researchers, we noted that appealing signs were visual loss and/or neurological complications including epilepsy,[36,37] memory troubles[38,39] and meningitis.[40,41] Psychiatric problems noted in some of our cases are also reported by others.[28,42] Obstructive hydrocephalus reported in anecdotic cases by Iglesias *et al*.[38] Scarone *et al*.,[43] and Alkatari and Aljohani[44] was relatively rare in our series, probably because of the tumor's slow progression. Spontaneous and post apoplexy comatose state, although exceptional, may be another manifestation in people with huge prolactinomas as we observed it.

Other uncommon manifestations such as hemi paresis, pyramidal and/or cerebellar syndrome and cranio-cervical junction instability[45] can be observed too.

Severe visual troubles are very frequent in our population. Blindness due to total optic atrophy is the most

troublesome complication. Other ophthalmological abnormalities such as strabismus and ptosis, observed in our work, are due to cavernous sinuses invasion and/or orbital infiltration. That one can be responsible for uni or bilateral exophthalmos.[20,46] Those uncommon ophthalmological complications disappear after tumor shrinkage secondary to bromocriptine or cabergoline intake. Although rare, reversible blindness can be observed after medical treatment too, especially in children and young people.[29,47]

Otorrhea and more commonly nasal bleeding can be induced by very large prolactinomas invading the skull base as observed by Chaurasia *et al*.[48] and in two of our cases in whom the diagnosis of prolactinoma was made by nasal biopsy.[49] In our experience orbital and nasal invasions were not seen in prolactinomas less than 4 cm in height.

It is very interesting to note that uncommon complications, even the life threatening ones, generally disappear after medical treatment as giant prolactinomas are known to be exquisitely sensitive to dopamine agonists.

Total or nearly total pituitary insufficiency is more frequent in large tumors in general. But in the study aforementioned, the difference was not significant between giant prolactinomas and those measuring <4 cm. Although somatotroph deficit was not systematically assessed by glucagon or insulin tolerance test, it appears that gonadotroph axis was the most sensitive to mass effect, followed by thyrotroph and corticotroph deficits. Those deficits may also improve under medical treatment.

Severe anemia due to pituitary insufficiency may reveal a giant prolactinoma as in one of our cases. Hematological troubles disappear[50] after prolactin normalization and hormonal substitution as we observed it.

Although prolactin is considered as an adipogenic hormone, obesity frequency noted in this study does not seem to be different from the one observed in our general population and in prolactinomas measuring less than 4 cm.

In this study, we noticed that gynecomastia is more frequent in giant prolactinomas than in smaller ones.[51] This may be explained by the profound hypogonadism characterizing giant tumors, and a nearly systematic radiological exploration of the breast based on echosonography and/or mammography in order to distinguish a true gynecomastia from an adipose tissue. Galactorrhea is also more frequently encountered the last ten years probably because of a better motivation or a better training of our team.

Conclusion

In this study concerning men harboring prolactinomas whose maximal diameter is superior or equal to 4 cm, optic atrophy, multiple endocrine deficits, and especially severe and life threatening neurological troubles are very frequent. But, obstructive hydrocephalus is relatively rare, which argues for a slow progression.

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