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## Gangliocytoma: outcome of a rare silent pituitary tumour

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# BMJ Case Reports

## Gangliocytoma: outcome of a rare silent pituitary tumour

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# BMJ Case Reports

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<b>TITLE OF CASE</b> <i>Do not include "a case report"</i>
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<b>Gangliocytoma: outcome of a rare silent pituitary tumour</b>
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<b>SUMMARY</b> <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i>
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The most common finding in front of a pituitary incidentaloma is a silent pituitary adenoma. We describe a 59 years old woman with a pituitary gangliocytoma and her follow up after one year. Hormonal exploration only evidenced partial corticotropic insufficiency. A transphenoidal surgery was performed due to the tumour's suprasellar expansion. Gangliocytoma is a benign tumour of unknown prevalence, belonging to CNS tumour with neuronal differentiation, and 129 cases have been reported in the literature. GH, ACTH or prolactin secretions have been reported, as these ganglion cell-like mature neurons are usually mixed with secreting pituitary endocrine cells. We report a case with a pure gangliocytoma devoid of symptomatic endocrine secretion, not surrounded by pituitary endocrine tumour cells. Immunocytochemistry of the tumour was positive for both hypothalamic GHRH and pituitary hormones, such as GH and ACTH. Hence, this immunorexpression was not associated with peripheral hormonal secretions, suggesting biologically inactive hypothalamo-pituitary hormones.

<b>BACKGROUND</b> <i>Why you think this case is important – why did you write it up?</i>
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Gangliocytoma is a benign pituitary tumour, which contains mature neurons resembling hypothalamic ganglion-like cells intermixed with a fibrillary background without glial tumoral component. This rare tumour of unknown prevalence and pathogenesis is now classified in the neuronal and mixed neuro-glial tumours section of the 2016 WHO CNS tumours classification [1]. Its prevalence is very low, as less than 130 cases have been reported in the literature [2,3]. It may be revealed either by an optic chiasm compression, or by

hormonal hypersecretion due to associated pituitary adenomas. Cases of acromegaly, precocious puberty and Cushing's disease have been reported in cases of gangliocytoma [4]. Histopathology shows ganglion cell-like mature neurons within an abundant neuropil matrix, composed of neurofibers and synapses. Positive immunohistochemistry on ganglions cells for GHRH, CRH, TRH, GnRH, somatostatin, VIP, or even pituitary hormones have previously been described [4]. Most cases are associated with endocrine anterior pituitary cells expressing GH, prolactin or ACTH.

We report an unusual case of a patient presenting with a pituitary gangliocytoma revealed as an incidentaloma, by a magnetic resonance imaging (MRI). Histopathology could not identify any endocrine anterior pituitary tumour cells. Interestingly, immunohistochemistry revealed that ganglion-like neurons themselves were positive for ACTH as well as GH and GHRH. This inactive hormonal secretion may illustrate altered processing or bioactivity of those hormones within the gangliocytoma. This rare tumour represents a differential diagnosis of a non-secreting pituitary tumour in front of a pituitary incidentaloma.

### **CASE PRESENTATION** *Presenting features, medical/social/family history*

A 59-year-old woman was referred to our endocrine unit for an incidentally discovered pituitary mass on encephalic MRI. This was performed as Sjögren syndrome was diagnosed in a context of inflammatory shoulder's arthralgia associated with headaches. She had delivered twice and experienced a normal menopause at the age of 50, with initial hot flushes shortly treated by paroxetine. Her only complaint was inflammatory shoulders' arthralgia at the time of the clinical examination in the endocrine unit. Her weight was 58 Kg and her height was 1.61m (BMI 22.4 Kg/m<sup>2</sup>). She had a normal blood pressure reaching 120/77 mmHg. Neither hypercortisolism nor acromegalic features were observed on clinical examination. She had no spontaneous nor provoked galactorrhea. She had no sign of diabetes insipidus.

### **INVESTIGATIONS** *If relevant*

Pituitary focused MRI revealed a 14x11x15 mm pituitary tumour, close to the left cavernous sinus. A slight infrasellar as well as a large type IV supra-sellar invasion, lifting up the optic chiasm was observed. A holosellar hyper-T1 signal (Fig 1), and an iso/hyper-T2 heterogeneous signal in the absence of gadolinium uptake were noticed. This contrasted with the hypo-T1 and T2 signals without gadolinium uptake present in most cases of silent pituitary adenoma [5]. Her visual acuity was normal and the absence of a bitemporal hemianopsia was confirmed by kinetic perimetry, carried out with Goldman's perimeter.

She was admitted in our department and hormonal investigations were performed. Her serum prolactin was 15 ng/ml (N: <27 ng/ml); urinary cortisol was 73 nmol/24h (N: <260); morning cortisol plasma level was 218 nmol/l (N: 220-610 nmol/l). Her plasma ACTH level of 51 pg/ml was at the upper limit of the normal range (N: <52 pg/ml). Plasma sodium and potassium were in the normal range. After tetracosactide (synacthen\*) test, her cortisol plasma level rose at 866 nmol/l (N after 60 mn: >550 nmol/l). TSH was 0.8 mUI/L (N: 0.4-4 mUI/L) and FT4 10.3 pmol/l (N: 7-18 pmol/l); alpha sub-unit plasma level was 2.84 UI/l (normal for menopausal women: N<1.6 UI/l), FSH and LH plasma levels were 62.5 and 52.1 UI/l respectively, with a low estradiol level of 22 pmol/l (normal for menopausal women: N<110 pmol/l). Plasma IgF1 was 160 ng/ml (N: 35-248 ng/ml). During an oral 75g glucose tolerance test, her plasma glucose rose to 8.3 mM and her lowest plasma GH was 0.4 mM after 120 min.

Hence, in front of the mildly low morning cortisolemia, hydrocortisone 10 mg per day was prescribed. Hypophysitis, in the context of Sjögren syndrome, could not be eliminated but no diabetes insipidus was present and no infundibulitis were noted on MRI.

### **DIFFERENTIAL DIAGNOSIS** *If relevant*

- . Silent gonadotropic pituitary adenoma,
- . Prolactinoma,
- . Acromegaly,
- . Intermittent Cushing's disease,
- . Hypophysitis.

**TREATMENT** *If relevant*

She was referred to our neurosurgeon in order to prevent optic chiasm compression, as a partially necrotic, non-secreting, suprasellar pituitary adenoma was suspected. Transphenoidal surgery was performed and the presence of a tumour capsule and a granular cell lesion were noticed by the experienced neurosurgeon. Removal of the tumour was considered sub-total, since a zone of close contact with the cavernous sinus was noticed.

Histology (Fig 2a and 2b) found a tumour exclusively composed of mature neurons with ganglion-cell aspect on a fibrillary background, with a fine vascularization and scattered zones of lymphocytic inflammation. Ki67 staining was 1%. No endocrine cell population was evidenced and some normally settled acini composed of corticotroph endocrine cells were seen, corresponding to the pars intermedia. Immunocytochemistry revealed a negative staining for prolactin, beta-TSH, beta-LH and beta-FSH, as well as Pit-1. Some ganglion cell-like neurons were positive for ACTH (Fig 2c) and cytokeratins (CAM5/2). A GH staining (Fig 2d) was present in a small proportion of the ganglion cells-like neurons but GHRH was diffusely expressed. Neuronal differentiation was also confirmed by synaptophysin, NF and chromogranin A immunopositivity.

**OUTCOME AND FOLLOW-UP**

The immediate post-operative period was marked by a transient insipidus diabetes, controlled with desmopressin treatment. Postoperative IgF1 serum level remained normal (175 ng/ml. N: 35-248 ng/ml) and corticotrophic insufficiency remained, as her postoperative morning cortisol level was 33 nmol/l with a plasma ACTH level of 13 pg/ml. Hydrocortisone treatment was therefore maintained. Three months later, persistent corticotrophic insufficiency was noted and we noticed a positive desmopressin test, as her cortisol rose from 134 to 282 nmol/l (47%, N: <20%) and ACTH rose from 16 to 30 pg/ml (53%, N: <35%), respectively. Nine months after neurosurgery, the patient was still on hydrocortisone for corticotrophic insufficiency: her last cortisol plasma level only rose from 72 nmol/l to 343 nmol/l (N after 60 mn: >550 nmol/l) after tetracosactide (synacthen\*) test. During another oral 75g glucose tolerance test, her plasma glucose rose to 8.1 mM and her lowest plasma GH was 0.3 mmol/l after 120 min. MRI revealed a stable millimetric paracavernous residue. One year after her initial consultation, she is now regularly monitored in order to detect a potential recurrence of the tumour.

**DISCUSSION** *Include a very brief review of similar published cases*

To date, 129 cases of gangliocytomas have been reported between 1990 and 2016 [2,3]. Since the exact pathogenesis was unknown, various authors used various ontologies in the past literature (ganglioneuroma, hamartoma, choristoma)[1]. Immune markers of both neuronal and glial cells have been identified in this particular tumour [4].

Few studies have addressed the origin of this tumour. One of the physiopathogenetic hypothesis relies on transdifferentiation of a common neuro-endocrine precursor or stem cell. Recently, an intriguing positive immunohistochemistry for anterior pituitary hormones on the ganglion cell-like component has been recently described [4]. In 2015, immunohistochemistry targeting a neuronal antigen protein have been also found on typical pituitary endocrine tumour: neuronal expression may also be an innate property of pituitary endocrine cells. The presence of ganglion cells inside pituitary endocrine tumour could represent a neuronal differentiation of an endocrine tumour, perhaps arising from an uncommitted progenitor cell [6].

In the literature, women are more frequently affected with gangliocytomas than men and acromegaly is the most frequent endocrine manifestation. The presence of a neural component does not seem to modify aggressiveness of the tumour or its risk of recurrence after resection [3]. No significant difference has been found between pure gangliocytoma and gangliocytoma mixed with pituitary endocrine tumor in terms of patients' characteristics [2], including age of onset, sex ratio, sellar mass syndrome, hormonology, (in)complete surgery. On MRI, authors have reported a sellar mass with hypoT1 signal (51% of cases), hyperT2 signal (69,6%), with less frequently cavernous sinus invasion (21%). Qiao described 23 patients, including 7 pure gangliocytoma [2]. Among them, three had

hyperprolactinemia and all were controlled at follow-up (mean: 4.2 years), either spontaneously or with bromocriptine. The same outcome was noted for one more patient with GH/Prolactin co-secretion. Finally, three patients without any significant hormonal hypersecretion did not recur at follow-up, but no detailed hormonal description was provided.

To our knowledge, this is the first report of a patient carrying a gangliocytoma without clinically significant hypersecretion, with a pure ganglion cell-like component, devoid of pituitary endocrine cell tumour, contrasting with positive immunochemistry for both hypothalamic and pituitary hormones (GHRH, GH and ACTH). Therefore, abnormal protein maturations and/or secretion of biologically inactive pituitary hormones in the neurons may explain the clinical setting.

**LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field**

- Gangliocytoma is a rare cause of pituitary tumour and knowledge on this topic is scarce. Its diagnosis may be difficult in the absence of any detectable hormonal secretion. Hence, it may be revealed by a pituitary incidentaloma. Its MRI characteristics may be close to those of silent pituitary adenomas.
- If a detectable hormonal secretion is present, then gangliocytoma is most frequently revealed by acromegaly, hyperprolactinemia or Cushing's disease.
- Gangliocytoma is a very rare tumour and its diagnosis is often performed during histological examination. The most frequent histological finding is a mix of ganglion cell-like neurons and pituitary endocrine cells.
- We describe a pure gangliocytoma: immunostaining was positive for ACTH, GH and GHRH. As it was not associated with peripheral hormonal secretions, this case suggests that hypothalamic and pituitary hormones from the tumour are biologically inactive.

**REFERENCES Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)**

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**FIGURE/VIDEO CAPTIONS figures should NOT be embedded in this document**

**Fig 1: Initial pituitary MRI of the 59 yrs old patient**

The pituitary MRI at presentation showed a type IV suprasellar mass of 14x11x15 mm, with a slight infrasellar invasion, very close to the optic chiasm. There was no obvious compression. On the T1-weighted sequence, a holosellar hyper-T1 signal was noted (A: upper image). No gadolinium uptake by this well limited mass (B: middle image), as well as an iso/hyper-T2 heterogeneous signal were noticed (C: lower image).

**Fig 2: Histopathology and immunochemistry**

**a)** x40 magnification – H&H stain: gangliocytoma. Histological examination showed a fibrillary background with abundant population of mature neurons resembling hypothalamic ganglion cells. A fine vascularization and scattered zones of lymphocytic inflammation were seen.

**b)** x100 magnification – H&H stain: large mature neurons ganglion cell-like within an abundant neuropil. Mature neurons presented with a voluminous round nuclei and an evident eosinophilic nucleoli as well as a strong eosinophilic granular cytoplasm. Rare bi-nucleations were observed.

**c)** x200 magnification – ACTH immunostaining: the ganglion cell-like neurons expressed ACTH in their cytoplasm.

**d)** x200 magnification – GH immunostaining: some clusters of ganglion cell-like neurons also expressed GH.

**PATIENT'S PERSPECTIVE *Optional***

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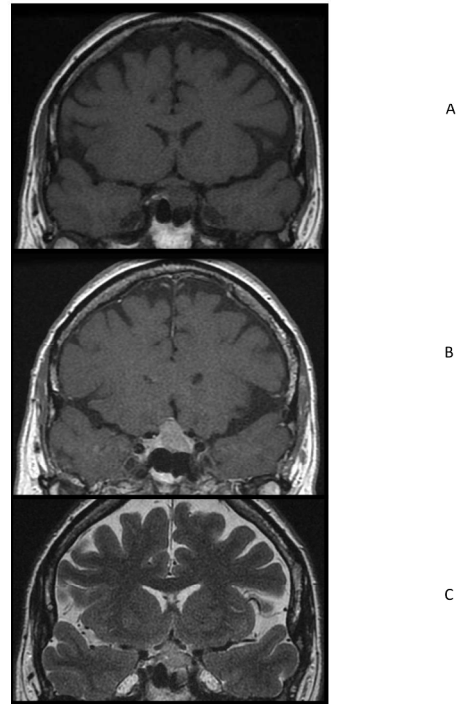


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Fig 1

209x297mm (300 x 300 DPI)



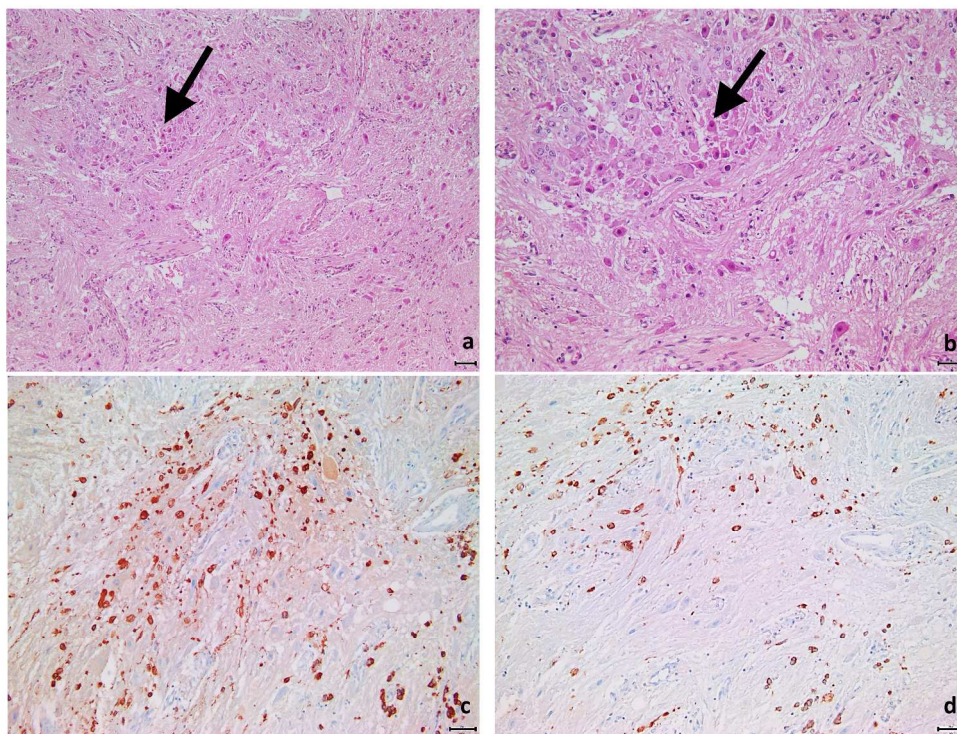


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- c) x200 magnification – ACTH immunostaining: the ganglion cell-like neurons expressed ACTH in their cytoplasm.
- d) x200 magnification – GH immunostaining: some clusters of ganglion cell-like neurons also expressed GH.

Fig 2a and 2b; Fig 2c; Fig 2d  
254x190mm (300 x 300 DPI)