Barts and The London
School of Medicine and Dentistry

Giant prolactinoma with JAK 2 positive mutation

Winnie Ho, Nicola Tufton, Maralyn Druce
Barts and the London School of Medicine & Dentistry, William Harvey Research Institute, St. Bartholomew's Hospital, Barts Health NHS TRUST, London

Introduction

- Giant prolactinomas represent 0.5% of all pituitary adenomas (1). They are characterized by their size (>40mm) and extremely high prolactin levels in the absence of GH or ACTH co-secretion (2).
- The male to female ratio is 9:1 (3). The most common presentations include visual field defect, headache, and sexual dysfunction, often with some degree of hypopituitarism. Rare presentations include seizure, hydrocephalus or epistaxis (1).
- The goals of treatment are to relieve acute compressive symptoms, reduce tumour mass, normalise prolactin levels, and preserve pituitary function (2).
- Cabergoline rapidly reduces prolactin levels and tumour volume. Surgery is reserved for patients with apoplexy or refractory cases. Temozolomide or radiotherapy should be considered in patients with clinically aggressive giant prolactinomas with uncontrolled mass effect despite multimodal therapies (4).

Case Report

- A 19-year old male presented with a generalized tonic-clonic seizure associated with visual loss. There was no significant past or family history. Examination revealed no vision in the left eye and right temporal temporal field loss and arrested pubertal development.
- Laboratory evaluation revealed a very elevated prolactin of 287 140 mU/L, hypopituitarism and essential thrombocytosis due to JAK 2 (V617F) mutation **(Fig 1, 2)**.
- Pituitary MRI revealed a large macroadenoma (58 × 40 × 28mm) exerting significant pressure on the optic chiasm, associated with acute hydrocephalus **(Fig 4)**. X-rays of the hands and wrist revealed delayed bone age of 16 years.
- The patient was diagnosed with a giant prolactinoma causing hydrocephalus, panhypopituitarism with arrested pubertal development. A diagnosis of JAK 2 essential thrombocytosis was also made.

Management and Progress

- Treatment was initiated with cabergoline 0.5mg daily, hydrocortisone 5mg BD, thyroxine 75mcg daily and testosterone sustanon 100mg monthly. After two weeks of cabergoline therapy, there was a 100-fold reduction in prolactin **(Fig 1)**. Prolactin levels steadily declined over 16 weeks and remained stable at 52 weeks **(Fig 2)**. Despite an impressive reduction in prolactin level and tumour volume **(Fig 3-5)**, there was no recovery of visual defects or hypogonadal axis. Given his young age of presentation, aryl-hydrocarbon-interacting protein (AIP) and multiple endocrine neoplasia 1 (MEN1) genetic mutation testing was performed, with results awaited.

Fig 1. Prolactin levels

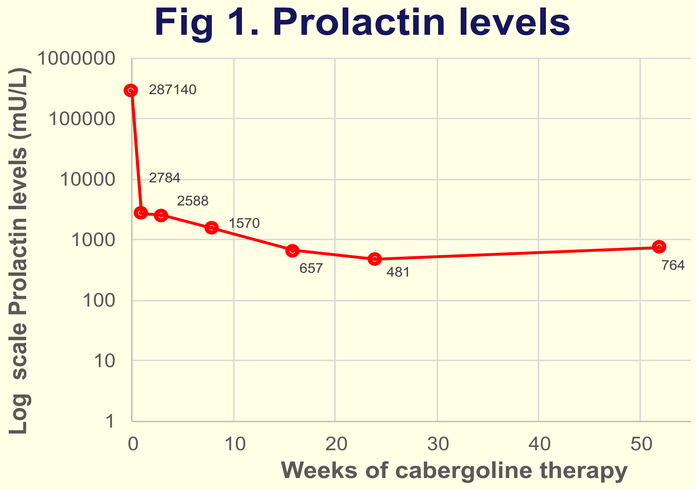


Fig 2. Laboratory results

	Baseline	At 52 weeks	Ref. range	Units
Prolactin	287 140	764 (nadir 481)	0-374	mU/L
ACTH 0900	36	47	<30	ng/L
Cortisol 0900	392	187	200-700	nmol/L
TSH	0.83	0.86	0.27-4.2	mU/L
Free T4	8.7	17.6	10.0-24.5	pmol/L
FSH	1.9	3.1	1.7- 8	U/L
LH	1.9	3.0	2-12	U/L
Testosterone	< 0.7	3.6	8.64- 29	nmol/L
Oestradiol	< 37	63	<190	pmol/L
SHBG	20		20-40	nmol/L
GH	<0.16		<0.6	mcg/L
IGF-1	112	154	120-885	**Units**
Platelets	817	1173	150-400	mU/L

Fig 3. Initial CT brain

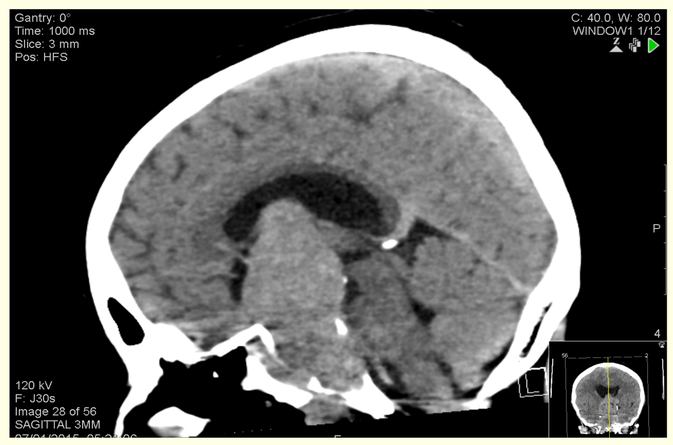


Fig 4. Initial MRI pituitary

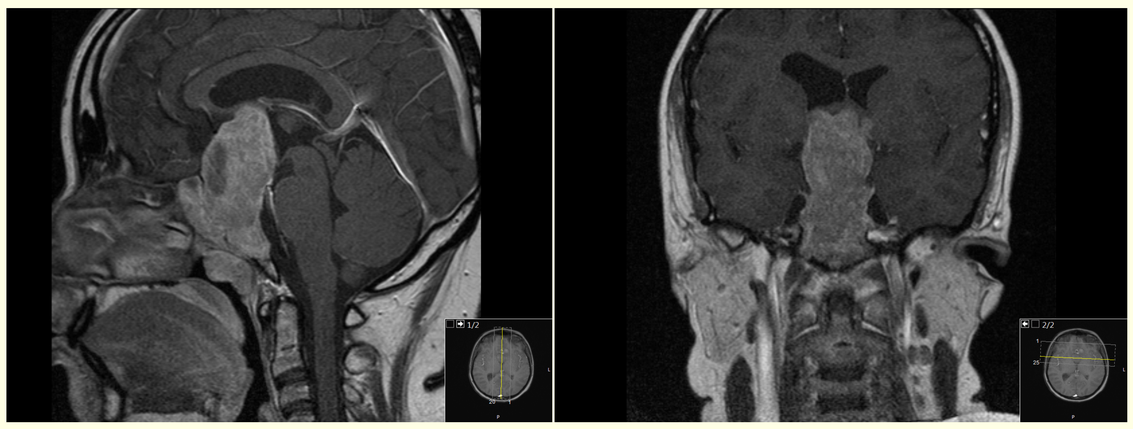
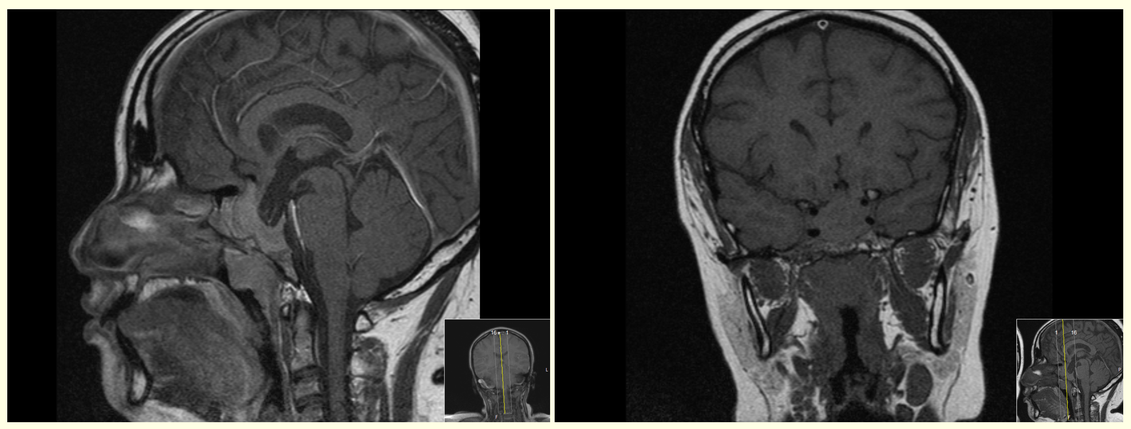


Fig 5. MRI pituitary after 52 weeks of cabergoline therapy



Discussion

- To our knowledge, this is the first case report of JAK 2 mutation with giant prolactinoma. Prolactin belongs to a family of cytokines (including GH, EPO, IL-6) which use the JAK-STAT signal transduction pathway to regulate cellular functions such as proliferation, differentiation, survival, and apoptosis (5). JAK2 has a role in endocrine and immune function, and STAT 3 and STAT 5 have been implicated in malignancies (6).Constitutional activation of the JAK STAT5 pathway is associated with hematological malignancies and primary tumours (breast, prostate, ovary, head and neck cancers) (7), however there has bene no previous account of lactotroph proliferation.
- Somatic JAK2 (V617F) mutation is found in 60% of patients with essential thrombocytosis or primary myelofibrosis and 95% of patients with polycythaemia vera (8). Patients with JAK2 essential thrombocytosis are at increased risk of arterial and venous occlusion as well as platelet-mediated haemorrhage.
- In a young patient presenting with macroprolactinoma, genetic testing for AIP and MEN-1 mutations should be considered (9).

Conclusion

- Cabergoline is effective first-line therapy for giant prolactinoma to rapidly reduce tumour size and prolactin levels.
- Coexistence of JAK 2 mutation and giant prolactinoma is rare, raising the possibility that constitutional activation of JAK2/STAT pathways may result in lactotroph proliferation. However, the interplay between various JAK/STAT pathways and cofactors are yet to be fully elucidated.

References

(1) Espinosa E et al. Giant prolactinomas: are they really different from ordinary macroprolactinomas? Endocrine. 2016 Jun;52(3):652–9 (2) Andujar-Plata P et al. Long-term outcome of multimodal therapy for giant prolactinomas. Endocrine. 2017 Jan;55(1):231–8 (3) Shimon I et al. Effectiveness of long-term cabergoline treatment for giant prolactinoma: study of 12 men. Eur J Endocrinol. 2007 Feb;156(2):225–31. (4) Moraes AB, Silva CM dos S, Vieira Neto L, Gadelha MR. Giant prolactinomas: the therapeutic approach. Clin Endocrinol (Oxf). 2013 Oct;79(4):447–56 (5) Rani A, Murphy JJ. STAT5 in Cancer and Immunity. J Interferon Cytokine Res. 2015 Dec 30;36(4):226–37 (6) O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in Immunity, Immunodeficiency, and Cancer. N Engl J Med. 2013 Jan 10;368(2):161–70. (8) Rumi E, Pietra D, Ferretti V, Klampfl T, Harutyunyan AS, Milosevic JD, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood. 2014 Mar 6;123(10):1544–51 (9) Korbonits M, Storr H, Kumar AV. Familial pituitary adenomas – who should be tested for AIP mutations? Clin Endocrinol (Oxf). 2012 Sep 1;77(3):351–6

BES2017 CC-002
Neuroendocrinology and pituitary
Winnie Ho
Poster presented at: SfE BES 2017 6-8 November HARROGATE
PosterSessionOnline.com