Endocrinology, Diabetes & Metabolism CASE REPORTS

J Bukowczan and others | Reversal of severe cognitive impairment

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Reversal of severe cognitive impairment following medical treatment of cystic invasive giant prolactinoma

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Summary

Giant prolactinomas are rare tumours of the pituitary, which typically exceed 40 mm in their largest dimension. Impairment of higher cognitive function has been noted post-operatively after transcranial surgery and as a long-term consequence of the radiotherapy treatment. However, there has been little that is reported on such disturbances in relation to the tumour *per se*, and to our knowledge, there has been none in terms of responsivity to dopamine agonist therapy and shrinkage in these tumours. We present a case of successful restoration of severely impaired cognitive functions achieved safely after significant adenoma involution with medical treatment alone.

Learning points:

- Giant prolactinomas can be present with profound cognitive defects.
- Dopamine agonists remain in the mainstay first-line treatment of giant prolactinomas.
- Mechanisms of the reversible cognitive impairment associated with giant prolactinoma treatment appear to be complex and remain open to further studies.
- Young patients with giant prolactinomas mandate genetic testing towards familial predisposition.

Background

Reversible cognitive impairment associated with the treatment of a prolactin-secreting pituitary adenoma has not been previously described. Herein we report the first case of an invasive giant prolactinoma causing a profound decline in the higher level executive cortical functions as a result of profound short-term memory impairment, which was substantially reversed following the institution of successful decompressive medical therapy.

Case presentation

A 22-year old maths university student was presented with a few weeks' history of mild headaches. He additionally reported a year's long history of gradual and progressive short-term memory deterioration, as evidenced by an unexpected poor performance at his recent examinations. In an attempt to compensate for the rapidly progressing memory problems, the patient started using 'smartphone' messaging and other memory cues. Subsequently, he found that he was receiving messages to remind him of the messages which he could not recall. This unusual and unexplained rapid decline in mentation with headache prompted an urgent MRI brain. It showed a large 48×52×28 mm midline hypervascular partially-cystic and partially solid sellar mass causing a significant brain compression with oedema, and extending into the suprasellar region with cavernous sinus invasion and chiasmal

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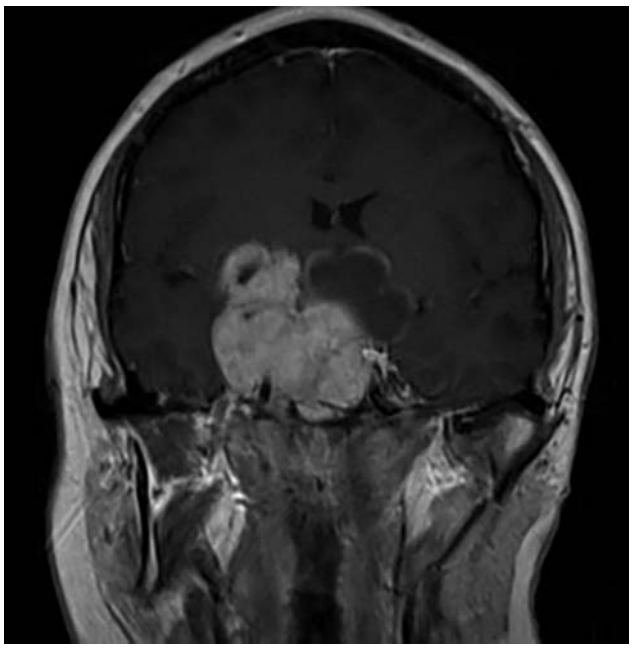

Figure 1
T1-weighted coronal MRI pituitary – view at presentation showing large 48×52×28 mm midline hypervascular cystic sellar mass causing significant brain oedema and extending into the suprasellar region with cavernous sinus invasion and chiasmal compression.

compression (Fig. 1). On direct questioning, he also complained of erectile dysfunction and decreased shaving frequency, but no galactorrhoea. On examination, he was clinically hypogonadal with significant gynaecomastia, sparse facial, chest and abdominal hair and Tanner stage IV pubic hair. His testes were soft and 20 ml in volume. A Humphrey visual field assessment showed a subtle left superior quadrantanopia. Extraocular eye movements remained intact, and visual acuity was normal.

Investigation

Urgent anterior pituitary function hormonal assessment revealed marked hyperprolactinaemia of 515 217 mIU/l (N: 0–450) and central hypogonadism (LH 0.9 IU/l (N: 1.8–8.2); FSH 2.1 IU/l (N: 1.4–14.0); testosterone 4.3 nmol/l (N: 6.7–25.7)). Other pituitary axes appeared to be normal (Table 1). Bone mineral density (BMD) confirmed osteopenia in the lumbar spine (Z-score: −1.9). A diagnosis of a giant invasive cystic prolactinoma with secondary hypogonadotrophic hypogonadism was made.

The patient completed a standard test of memory, new learning and memory as a baseline. The standard scores were based upon a T distribution with a mean of 50 and s.d. of 10. The neuropsychological assessment with BIRT Memory and Information Processing Test Battery revealed profound cognitive impairment (Table 2, column 1), as shown by significantly reduced immediate and delayed figure recall (T score with percentiles were 43, 25 and 35, 7 respectively), design learning (T score: 42, percentile: 20), immediate story recall (T score: 33, percentile: 4), delayed story recall (T score: 32, percentile: 4), and list learning (T score: 39, percentile: 14). The first four scores evaluated functions of learning and retention of complex information, which were very weak. Additionally, some elements of confusion with a degree of confabulation were noted. Despite significant deficiencies in the initial learning of written information as demonstrated in the list of learning and design learning tasks, the patient showed a relatively normal learning curve with a positive improvement on each repetition of material. The overall impression was that the cognitive difficulties appeared to be more complex than a straightforward problem of memory and

Table 1 Endocrine assessment at baseline, 6 and 12 months following treatment.

Test	Presentation	6 months	12 months	Reference range
Prolactin (mIU/l)	515 217	6454	448	0–450
TSH (mU/l)	0.78	1.56	2.13	0.3–4.7
Free T_4 (pmol/l)	15.2	13.4	13.3	9.5–21.5
Free T_3 (pmol/l)	3.8	4.4	4.2	3.5–6.5
LH (U/l)	0.9	2.5	2.1	1.8–8.2
FSH (U/l)	2.1	4.3	3.3	1.4–14.0
Testosterone (nmol/l)	4.3	10.1	14.6	9–25
GH (μg/l)	<0.1	<0.1	<0.1	<3.1
IGF1 (nmol/l)	15	18	17	5–26
0900 h Cortisol (nmol/l)	510	–	–	170–540
Short Synacthen Test (cortisol; nmol/l)	0 – 238 30′– 713 60′– 797	0 – 353 30′– 568 60′– 610	0 – 351 30′– 744 60′– 825	170–540

GH, growth hormone; IGF1, insulin like growth factor 1; LH, lutenizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; free T_3, free triiodothyronine; free T_4, free thyroxine.

Table 2 Neuropsychological assessment using BIRT Memory and Information Processing Test Battery at presentation and 6 months following treatment.

	At presentation		After 6 months of treatment		Reference range	
	T Score	Percentile	T Score	Percentile	T Score	Percentile
Figure immediate	43	25	66	94	>52	>60
Figure delayed	35	7	61	87	>50	>60
Design learning	42	20	60	85	>48	>60
Story immediate	33	4	57	76	>45	>60
Story delayed	32	4	59	82	>43	>60
List learning	39	14	71	98	>45	>60

new learning. Formal diagnosis of profound cognitive impairment of unknown aetiology was made.

Treatment

The patient was commenced on cabergoline 250 μg weekly, which he has been taking until present.

Outcome and follow-up

The patient's prolactin levels were rapidly reduced to 119 583 mIU/l after the first two doses, and further to 56 061 mIU/l by week 4. No side effects or complications of treatment were reported. A 3-month follow-up MRI showed a very significant reduction in tumour size (Fig. 2). Serum prolactin levels fell by 99% within 6 months of treatment, and patient was maintained on low dose cabergoline (250 μg weekly) thereafter until now. The AIP and MEN genes mutation analyses were proved negative. A detailed repeated psychometric assessment performed 6 months following the commencement of dopamine agonist showed complete resolution of cognitive dysfunction (Table 2, column 2). On three of the four memory tasks, the patient obtained a score at the upper limit for the test, and was deemed to perform within the superior range of ability. The patient has since successfully completed his Masters in Mathematics course and is now working on his PhD in Maths and Computing.

Discussion

Reversible cognitive impairment associated with the treatment of a prolactin-secreting pituitary adenoma has not been previously described. Herein, we report the first case of an invasive giant prolactinoma causing a profound decline in the higher level executive cortical functions as a result of profound short-term memory impairment, which was substantially reversed after following the institution of successful decompressive medical therapy.

There were no contributory endocrinopathies, which could be associated with this pattern of impaired cognition. Interestingly, local pressure effects to the surrounding brain area by the patient's giant prolactinoma share homology with midbrain arachnoid cysts, which notably have been reported to cause reversible cognitive impairment upon surgical decompression (1, 2, 3). In a prospective cohort study, Raeder *et al.* (4) showed that although intracystic pressure of arachnoid cysts remained within the limits of normal intracranial pressure, there was a significant correlation between the intracystic pressure and the preoperative level of impaired mental

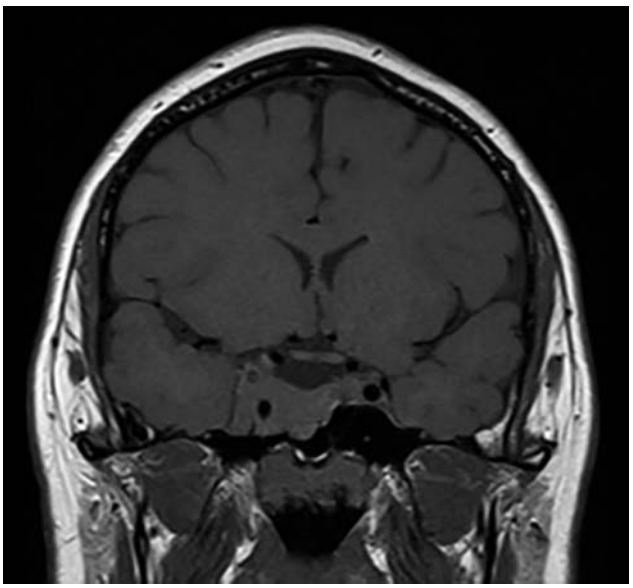

Figure 2
T1-weighted coronal MRI pituitary – view following 6 months of cabergoline treatment showing significant tumour shirinkage.

function. Neuroimaging studies proved that arachnoid cysts may affect local perfusion and metabolism, and that those changes can be reversed following cyst decompression, which were also evidenced by clinical and cognitive assessments.

Our patient showed a remarkable recovery from his initially very low scores after just 6 months of cabergoline treatment, allowing him to study for a high-level degree, and associated with a dramatic tumour involution with reduction in pressure on key brain structures, and has remained well until present. Moreover, a 6-month follow-up pituitary MRI confirmed complete resolution of cystic giant prolactinoma.

One final aspect to consider is that a large prolactinoma in a young individual may represent the first manifestation of a MEN-1 syndrome, or be related to a genetic predisposition to develop familial pituitary adenomas. Appropriate genetic testing is, therefore, highly recommended in such cases (5).

In conclusion, giant prolactinomas can be presented with profound cognitive defects because of the local compressive effects. They can also masquerade as other causes of cognitive impairment include arachnoid cysts. Cabergoline was the effective and safe first-line treatment, which, by inducing dramatic tumour shrinkage, resulted in immediate and complete resolution of debilitating cognitive impairment.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
A written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement
J Bukowczan was involved in patient's care, collected data, wrote the manuscript and submitted the manuscript; K Lois was involved in patient's care and contributed to the discussion; M Mathiopoulou was involved in patient's care and contributed to the discussion; R A James was the named consultant supervising patient's care from the outset, oversaw the manuscript and contributed to the discussion; A B Grossman is currently involved in patient's follow-up as the patents moved to a different Trust, edited the manuscript and contributed to the discussion.

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