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The High-Dose Dopamine Agonist Treatment Induced Pituitary Apoplexy: A Case Report

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1. Abstracts

Pituitary apoplexy is a rare condition especially caused by the hemorrhage or infarction of the pituitary macroadenoma. Hereby, we present a case of macroprolactinoma treated with dopamine agonist with bromocriptine leading to pituitary apoplexy.

1.1. Case Presentation

This is a case of a 51-year-old male who presented at West China Hospital of Sichuan University with complaints of severe headache and dizziness persisting for 6 months. The patient's prolactin level (PRL) was measured at 3840ng/ml. A magnetic resonance imaging (MRI) scan of the sella turcica region revealed an enlarged pituitary fossa with a soft tissue mass measuring approximately 3.2cm×2.6cm×2.1cm in size. Based on the patient's medical history, physical examination, MRI findings, and other blood test results, a diagnosis of macroprolactinoma was established. The patient was initiated on a treatment regimen of Bromocriptine (BRC) at a dosage of 5mg two times daily for 30 days. As the symptoms gradually improved, the dosage was adjusted to 5mg daily. Subsequently, the prolactin level was significantly reduced to 0.3ng/mL along with shrinkage in tumor size, thus we suspected that pituitary apoplexy experienced by this patient may be attributed to the rapid decline in PRL levels and the subsequent rapid shrinkage and hemorrage of the pituitary gland during treatment with dopamine agonists. Currently, the MRI and PRL level (11ng/mL) were within normal limits.

1.2. Conclusion

Establishing a collaborative diagnosis and treatment model involving a multidisciplinary team is key to enhancing the diagnosis and prognosis of macroprolactinoma with pituitary apoplexy, ultimately improving the outcomes of patients.

2. Introduction

Macroprolactinomas are pituitary tumors ≥ 10mm in diameter with serum prolactin levels greater than 235 µg/L (5000 mU/L) [1]. Pituitary adenomas are classified as micro prolactinoma (<10mm), macroprolactinoma (≥10mm), and giant prolactinoma (≥40mm) based on the size of the tumor. Pituitary apoplexy (PA) is a rare condition primarily caused by ischemia or hemorrhage of large, non-functional pituitary adenomas. However, PA has rarely been reported in cases of microadenomas [2]. The incidence and prevalence of pituitary apoplexy in macroprolactinoma were as high as 55.6% and 6.2 cases per 100000 population respectively [3]. Development of clinical apoplexy can be seen in around 2-12% of patients with pituitary adenomas [4, 5].

The clinical syndrome of pituitary apoplexy includes headache (mostly abrupt), vomiting often accompanied by headache, visual field and visual acuity defects resulting from the upward extension of the tumor which compress the optic chiasma, optic tracts, or optic nerve [4, 6, 7]. It has a male-to-female ratio of 2:1 and the age range is 37-57 years [8]. There is still no obvious etiology of pituitary apoplexy mentioned in the literature but factors such as brain trauma, medical therapy (dopamine agonists), radiotherapy, anticoagulation or antiplatelet therapy, previous surgery, etc are believed to induce pituitary tumor hemorrhage and subsequently pituitary apoplexy [9, 10]. Corncerning the specific pituitary adenoma responsible for apoplexy, there is inconsistency in the

data. Some studies have indicated a higher occurrence of pituitary apoplexy in non-functioning tumors. [11, 12]. Other studies also indicate a higher prevalence among functioning tumors [13, 14]. Prolactinomas demonstrated the highest prevalence among the secreting tumors [12]. Even though there are many precipitating factors, the pathogenesis is not implicated. Managing pituitary apoplexy poses a diagnostic and therapeutic challenge, primarily due to the absence of widely adopted specific guidelines. Thus, a case of macroprolactinoma resulting in pituitary apoplexy after bromocriptine treatment is reported in this article.

3. Case Presentation

A 51-year-old Chinese male presented to the outpatient department of West China Hospital of Sichuan University with complaints of severe headache and dizziness for 6 months. There was no significant history of visual problems, nausea, vomiting, galactorrhea, hypogonadism, and gynecomastia. There were no significant changes in appetite, weight, bowel and bladder habits. On ophthalmological examination, there were no visual field defects, diplopia, or loss of vision. The blood test done 2 months before presenting to our hospital showed the PRL level was 3840ng/mL (4.6-21.4), testosterone (T) level 1.14ng/mL (2.6 - 8.64ng/mL), growth hormone (GH) 0.71ng/mL (0.03-2.47), insulin-like growth factor-1 (IGF-1) 90.55ng/mL (111.4-256.8), thyroid stimulating hormone (TSH) 5.570mU/L (0.27-4.2), free tri- iodothyronine (T3) 4.20pmol/L, free thyroxine (T4) 11.60pmol/L (12.0-22.0), luteinizing hormone (LH) 1.3IU/L (1.7-8.6), follicle-stimulating hormone (FSH) 2.3IU/L (1.5-12.4), serum cortisol (PTC) 340.00nmol/L (147.3-609.3), adrenocorticotropin (ACTH) 46.03ng/L (147.3-609.3). The MRI scan of the sella turcica conducted in our hospital revealed a macroadenoma with dimensions of 3.2cm×2.6cm×2.1cm. The mass exhibited poor demarcation from the bilateral cavernous sinuses, causing mild compression of the optic chiasm. Thinning of the bone in the sellar floor was observed in figure1(A, B). Based on clinical history, physical examination, MRI, and other blood reports the diagnosis was made as macroprolactinoma.

4. Treatment and Follow-Up

The patient has treated with BRC 5mg two times a day for 30 days, his symptoms were gradually relieved and the medicine dose was gradually decreased to 5 mg per day and the size of the tumor shrank noticeably. The blood reports after 2 months of initiating treatment showed the PRL level was 0.3ng/ml; T level 2.4 ng/mL, dehydroepiandrosterone sulfate 4.510 umol/L, LH 5.3 IU/L, FSH 4.4 IU/L, ACTH 41.36 ng/L, PTC 262 nmol/L, GH 0.56ng/ml. The MRI, conducted a few months after medical treatment, revealed pituitary apoplexy with an ultramicroadenoma in Figure 1 (C, D). We suspect that Pituitary apoplexy in this patient may be related to the rapid decline of PRL and the quick shrinkage of the pituitary gland during treatment with dopamine agonists. The dosage of BRC was adjusted to BRC 1.25 mg twice a day. The patient was followed every month for monitoring PRL level. The PRL level decreased from 0.3ng/ml to 0.22ng/mL in one month then again decreased to 0.19ng/ml in consecutive months. Thus, the dosage was further adjusted to BRC 1.25 mg once a day. The PRL level was increased to 1.46ng/mL after 4 months of treatment. Now, the patient's Prolactin level (11.7ng/ml) along with other laboratory reports and MRI in figure 1(E, F) are normal after effective medical treatment. The patient's hormonal profile is presented in Table 1. Throughout the follow-up period, the patient's overall health, sleep pattern, weight, appetite, urination, and bowel movements remained within normal parameters. Consequently, the medication was ultimately discontinued.

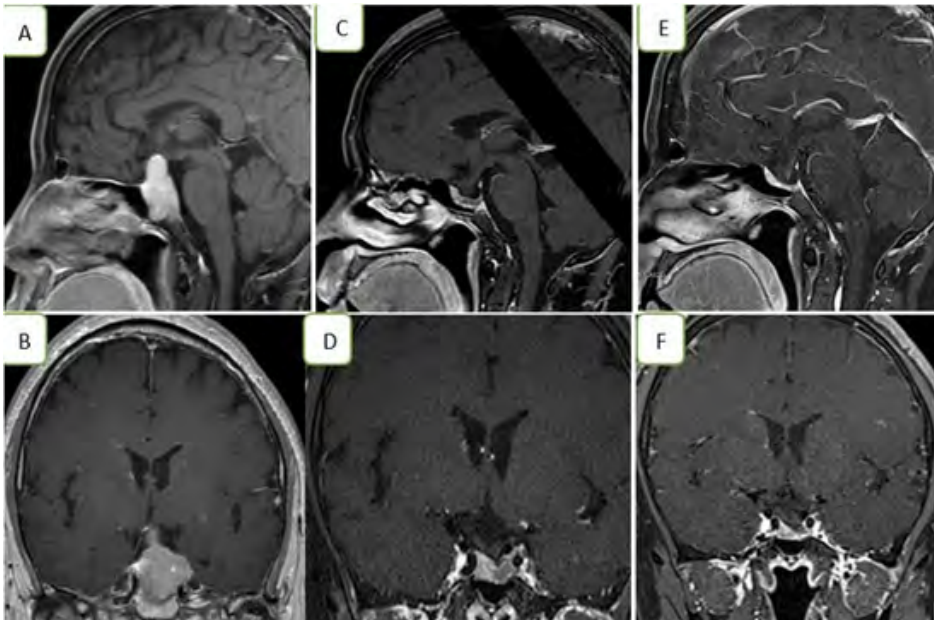

Figure 1: MRI: Before and after treatment with bromocriptine.

Table 1: Comparision of the hormonal panel before and after treatment with dopamine agonists.

Test	Initial Value	after 6 months of treatment	after 3 years of treatment	Normal range
PRL (ng/mL)	3840	0.19	11.7	4.6-21.4
T (ng/mL)	1.14	2. 4	2.86	2.6 -8.64
(GH) (ng/mL)	0.71	3.31	0.42	0.03-2.47
IGF-1(ng/ml)	90.55	-	204	111.4-256.8
TSH (mU/L)	5.57	4.48	4.5	0.27-4.2
T3 (pmol/L)	4.2	-	-	3.6-7.5
T4 (pmol/L)	11.6	13.7	14.4	12.0-22.0
LH(IU/L)	1.3	5.3	5	1.7-8.6
FSH(IU/L)	2.3	4.4	5.4	1.5-12.4
PTC (nmol/L)	340	262	262	147.3-609.3
ACTH (ng/L)	46.03	41.36 ng/L	33.13	147.3-609.3

Abbrebiations: Prolactin (PRL); Testosterone (T); Growth hormone (GH); Insulin-like growth factor-1 (IGF-1); Thyroid stimulating hormone (TSH); Free Tri-iodothyronine (T3); free Thyroxine (T4); Luteinizing hormone (LH); Follicle stimulating hormone (FSH); Serum Cortisol (PTC); Adrenocorticotropin hormone (ACTH).

5. Discussion

The pathophysiology of pituitary apoplexy is not yet clear but is likely to have multiple causes [15]. Rapidly growing tumors can also elevate intrasellar pressure, leading to venous outflow issues and subsequent hemorrhaging. The lack of vascular supply can cause ischemia and subsequent necrosis in the anterior pituitary gland and the tumor itself, resulting in an apoplectic event. The use of dopamine agonists, whether at the initiation of treatment or upon its discontinuation, has been associated with a contributing role [16]. Particularly concerning this case, PA may have been caused by the impaired blood supply to the pituitary adenoma. We suspect that the rapid decline of the PRL level and the rapid shrinkage of the pituitary gland after the treatment with dopamine receptor agonists may be the primary reason. The restoration of varying degrees of the pituitary and visual functions has been confirmed in many reports with the shrinkage in the volume of the pituitary adenomas [17]. However, in these types of cases where the patient's prolactinomas cause a sudden increase in hemorrhage volume due to stroke, resulting in mild optic nerve compression but no other substantial occupying effects, may give rise to severe complications like anterior hypopituitarism or potentially pituitary crisis.

Pearce Bailey recorded the first occurrence of bleeding linked to a pituitary tumor in 1898. However, it wasn't until 1950 that Brougham et al. introduced the term "pituitary apoplexy," which includes both necrosis and bleeding within pituitary tumors [18]. Approximately 25% of all pituitary adenomas exhibit areas with hemorrhage and/or necrosis [19]. From a clinical perspective, the symptomatic profile of pituitary apoplexy is categorized into three dimensions: visual, endocrine, and headache. During its acute presentation, common manifestations include headache (73%), reduced visual acuity (68%), hypopituitarism (64%), visual field defects (49%), nausea (49%), diplopia (ophthalmoparesis, 48%), and, to a lesser degree, an altered state of consciousness (17%), which may involve nuchal rigidity and resemble an intracranial hypertension syndrome. Nevertheless, approximately 25% of patients exhibit subclinical or asymptomatic conditions.[20]. The prevalent abnormalities associated with subclinical pituitary apoplexy typically involve thyroid and adrenal dysfunction [14]. This patient also showed no symptoms of pituitary apoplexy, indicating asymptomatic pituitary apoplexy. Possible causes of pituitary apoplexy include both functioning and nonfunctioning tumors of the pituitary, with prolactin-producing adenomas (prolactinomas) being more common. Additionally, cysts of the Rathke cleft contribute to these etiologies. Among them, certain triggers are identified in 10%-40% of patients, including hypertension, major surgery, dynamic tests involving growth hormone (GH), thyroid- stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH), hormone replacement therapy, third- trimester pregnancy, head trauma, and angiographic procedures [21, 22]. The pituitary apoplexy has been seen in a majority of cases of adult pituitary adenomas, thus the medical approach using dopamine agonists has become the first line of treatment for macroprolactinomas. As PA is a medical emergency, immediate management by assessing and managing fluids and electrolyte balance, ensuring hemodynamic stability, and corticosteroid therapy are very important. The expert multi-disciplinary team should be consulted for further medical or surgical management [23]. All patients should receive corticosteroid treatment even if they do not present symptoms of adrenal crisis. The proper assessment of anterior pituitary and visual function should be done at 4-6 weeks, which suggests the replacement of an adequate dose that helps to improve the vision and restore the visual field. The follow-ups should be maintained for 6-12 months for monitoring and optimization of the treatment and assessing the recurrence or progression of the tumor [24]. In our case, the patient underwent dopamine agonist treatment with bromocriptine only, without any hormonal replacement therapy or steroids treatment. Ficnally, after more than two years of follow-up, the patient's medication was ceased and the general condition of the patient was good.

6. Summary

In conclusion, the predisposing factors of pituitary apoplexy are diverse and a small percentage of individuals experiencing pituitary apoplexy will have identifiable precipitating factors. Therefore, it is important to avoid these predisposing factors including stimulation of the pituitary, treatment with bromocriptine or cabergoline, gonadotropin-releasing hormone treatment, anti coagulant, pregnant, undergoing pituitary irradiation etc. The prognosis of pituitary apoplexy is closely linked to the course and severity of the disease at onset, and whether the treatment is timely and appropriate. Thus, timely and effective treatment greatly contributes to improving the prognosis of pituitary adenoma apoplexy. Developing a collaborative diagnosis and treatment model involving a multidisciplinary expert team, such as neurosurgery for potential surgical therapy, medicine for general medical management, endocrinology for hormonal management, and ophthalmology for assessing visual acuity, perimetry, and motility is beneficial for enhancing the diagnosis and prognosis of patients with macroprolactinoma complicated with pituitary apoplexy.

7. Strengths and Limitations

Our case report incorporates distinctive clinical characteristics to present a comprehensive clinical history, laboratory reports encompassing present, as well as treatment details and outcomes till now in our out patient department with normal Prolactin level and MRI without any medication having healthy lifestyle. However, it is important to acknowledge the limitations of our study, including the absence of hormonal panel test results during 3 months after the treatment. (A) T1 weighted sagittal and (B) coronal images of macroadenoma with 3.2cm×2.6cm×2.1cm size. The mass exhibited poor demarcation from the bilateral cavernous sinuses, causing mild compression of the optic chiasm. Thinning of the bone in the sellar floor was observed, and there was no enlargement of the supratentorial ventricle before treatment (C). T1 weighted sagittal image and (D) coronal image revealed pituitary apoplexy with an ultramicro small adenoma. The pituitary fossa appeared enlarged, with slightly decrease in enhancement noted on the left side. The optic chiasm showed slight thickening and downward displacement. Moreover, a significant reduction in the size of the tumor was observed compared to the previous MRI film after treatment. (E) T1 weighted sagittal and (F) coronal image revealed adenoma was reduced without any compression of adjacent tissues after two years of treatment.

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