Case Report

Secondary resistance to bromocriptine and cabergoline therapy in hyperprolactinemia: One case of pregnancy with IVF-ET

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Abstract

Background: For patients with hyperprolactinemia, primary dopamine agonist resistance occurs in 10-15%, secondary resistance following initial biochemical and anti-proliferative response is very rare and has only been described in five previous cases. For women of childbearing age, hyperprolactinemia affects follicular development, potentially causing infertility. Currently, reports on pregnancy outcomes of secondary dopamine resistance in patients with unexplained hyperprolactinemia are scarce. In this paper, we report one case of pregnancy with unexplained bromocriptine- and cabergoline-resistant hyperprolactinemia, with follow-up data for four years after birth.

Case report: The 32-year-old patient had been diagnosed with primary infertility for four years. She has been treated with dopamine agonist therapy for 3 years. At first, she was initially treated with bromocriptine, marked reduction in prolactin concentration. After one years her prolactin concentration began to rise despite escalating doses of bromocriptine up to six tablets/day and cabergoline up 6mg weekly(two tablets each time, three times per week). Hypothalamic-pituitary lesions and other lesions were ruled out. After ovulation induction, the development and ovulation of dominant follicles were observed only occasionally. The patient failed to become pregnant after intrauterine insemination (IUI) . However, after one cycle of IVF-ET(in vitro fertilization-embryo transfer)the patient became pregnant. She delivered a baby girl at full term, and the baby was normal over the course of the four-year follow-up.

Conclusion: While the mechanism of secondary resistance remains unknown and not possible to predict, the woman can become pregnant after IVF-ET, even if the PRL level remains higher than normal.

Abbreviations: PRL-Prolactin; IUI-Intrauterine Insemination; IVF-ET-In Vitro Fertilization-Embryo Transfer.

Introduction

Prolactin (PRL) is an important hormone involved in regulating the gonadal axis. Hyperprolactinemia is a syndrome of hypothalamic-pituitary axis reproductive and endocrine disorders that is associated with many causes and is characterized by high serum prolactin (PRL) levels and related clinical manifestations. Hyperprolactinemia involves the reproductive, endocrine, and nervous systems and is common in clinical practice. The incidence rate of hyperprolactinemia is 23.9/100 000 each year in 25- to 34-year-old women. Hyperprolactinemia causes gonadotropin deficiency and thus hypogonadism, resulting in menstrual cycle disorders, infertility, and/or galactorrhea [1]. In most cases, a dopamine agonist is used as a first-line treatment for most types of prolactinoma to reduce the PRL level and tumor size [2]; 80% to 90% of patients resume ovulation after treatment [3]. However, for some prolactinoma patients, the PRL level remains high with no tumor shrinkage after treatment with a high-dose of dopamine agonist, suggesting dopamine resistance [4]. A dopamine agonist is usually effective for treating idiopathic hyperprolactinemia [5]. In clinical practice, we treated one patient with unexplained hyperprolactinemia who was resistant to both bromocriptine and cabergoline. At first, she was initially treated with bromocriptine, marked reduction in prolactin concentration. After one years her prolactin concentration began to rise despite escalating doses of bromocriptine up to six tablets/day and cabergoline up 6mg weekly(two tablets each time, three times per week). The patient failed to become ovulation induction and IUI. She finally got pregnancy after IVF-ET.; Her baby was followed up for four years after birth. In this paper, we report case data from the patient and perform a literature review of related cases.

History of illness

Patient's basic history of illness

The patient was female, 32 years old, with a body mass index (BMI) of 17. In April 2010, she visited our hospital for the "inability to become pregnant after being married for four years without the use of birth control methods." An inquiry into her detailed history revealed that her menstrual cycle started at 14, with irregular menstruation that required medication for regulation. Tubal examination showed patent tubes. Semen test results of her husband were normal.

Endocrine results and hyperprolactinemia-related tests

A previous D3 hormone test at a local hospital showed a PRL level of 300 ng/mL; after treatment with bromocriptine, four tablets/day,

her PRL level can reduce to 30 ng/mL. After one years her prolactin concentration began to rise despite escalating doses of bromocriptine up to six tablets/day Therefore, the patient's treatment was changed to cabergoline, two tablets/day, PO, three times per week. After treatment, a sex hormone test revealed a follicle-stimulating hormone (FSH) level of 2.13 mIU/mL, a luteinizing hormone (LH) level of 0.52 mIU/mL, a PRL level of 115.2 ng/mL, a progesterone (P) level of 0.98 ng/mL, and an estradiol (E2) level of 9.14 pg/mL. Brain computed tomography and magnetic resonance imaging (per a neurosurgeon's recommendation) were normal. The patient's thyroid and adrenal glands were normal, and her visual field was normal. The patient complained of severe galactorrhea, with no significant growth of body hair. After treatment with a higher dose of cabergoline, the patient reported intolerable nausea, vomiting, and worsening dizziness, so the dose was reduced to the original level.

Ovulation induction

Repeated ultrasound B exams at a local hospital revealed no visible development or ovulation of dominant follicles. Given her irregular menstruation, the patient was pre-treated with medications (progynova + progesterone) to induce two artificial cycles, and she continued to take cabergoline. After two cycles of treatment, her PRL was 105.7 ng/mL. With patient consent, 50 mg of clomiphene citrate was given to induce ovulation for two cycles (day five of the menstrual cycle, one capsule, PO, QD). During cycle one, dominant follicles were developed to 19.4 mm, and the endometrial thickness was 7.1 mm/type B. Hormone tests returned a serum E2 level of 473.914 pg/mL, an LH level of 15.2 mIU/mL, a P level of 0.61 ng/mL, and a PRL level of 99.01 ng/mL. The patient was given an intramuscular (IM) dose (10 000 IU) of human chorionic gonadotropin (HCG) and was then instructed to have sexual intercourse. Luteal support was given after follicle rupture. Fourteen days later, the serum β-HCG level indicated that the patient had failed to become pregnant. During cycle two, dominant follicles were developed to 18.9 mm, and the endometrial thickness was 6.7 mm/type B. Hormone tests returned a serum E2 level of 403.4 pg/mL, an LH level of 16.8 mIU/mL, a P level of 0.52 ng/mL, and a PRL level of 117.9 ng/mL. The patient was given an IM dose (10 000 IU) of HCG and was then instructed to have sexual intercourse. Ultrasound B showed that the follicles luteinized but did not rupture. During cycle three, human menopausal gonadotropin (hMG) was given to induce ovulation (day three of the menstrual cycle, 75 IU, every other day, for a total of five injections). Dominant follicles were developed to 19.8 mm, and the endometrial thickness was 8.8 mm/type B. Hormone tests returned a serum E2 level of 313.6 pg/mL, an LH level of 12.8 mIU/mL, a P level of 0.47 ng/mL, and a PRL level of 107.81 ng/mL. The patient was given an IM dose (10 000 IU) of HCG and was then instructed to have sexual intercourse. Luteal support was given after follicle rupture. Fourteen days later, the serum β-HCG level indicated that the patient had failed to become pregnant. During cycle four, hMG was given to induce ovulation (day three of the menstrual cycle, 75 IU, for a total of 12 injections). No obvious development of dominant follicles was observed.

Intrauterine insemination (IUI)

The patient insisted on receiving assisted reproductive treatment. Given her condition, IUI was recommended. After treatment to induce two artificial cycles, a higher dose of hMG was given to induce ovulation. During cycle one, the development and ovulation of dominant follicles was observed, and IUI and luteal support were given. However, the patient failed to become pregnant. During cycles two and three, hMG

was given to induce ovulation, and an IM dose (10 000 IU) of HCG was then given after the development of dominant follicles. However, the follicles luteinized but did not rupture.

IVF-ET (In vitro fertilization-embryo transfer)

We advised the patient to reduce her mental stress and planned to perform IUI after additional ovulation induction. The patient declined additional IUI and insisted on receiving IVF. We developed a plan with a longer timeline. After the induction of artificial cycles, gonadotropin-releasing hormone agonist (GnRHa; triptorelin) was given on day 25 of the menstrual cycle (0.1 mg, subcutaneous injection, for 18 days). Hormone tests returned a serum E2 level of 9.14 pg/mL, an LH level of 0.52 mIU/mL, a P level of 0.98 ng/mL, and a PRL level of 115.2 ng/mL. Then, 150 IU of β-FSH was given for 12 days to induce ovulation. By the time of HCG dosing, eight follicles were larger than 14 mm. Hormone tests returned a serum E2 level of 2,568 pg/mL, an LH level of 0.58 mIU/mL, a P level of 1.71 ng/mL, and a PRL level of 171.2 ng/mL. HCG (8000 IU) was given to induce ovulation, and eggs were collected 36 hours and 25 minutes later. A total of 10 eggs were collected, of which seven were in metaphase II (MII); five were fertilized, and five embryos were considered viable (4c, 5% fragments; 8c, 10% fragments; 6c, 10% fragments; 8c, 20% fragments; 9c, 20% fragments). Two considered viable embryos were implanted on day three after egg collection. Luteal phase support was given on the day of embryo transfer . Additional embryos considered viable according to morphologic criteria were frozen for later transfer in subsequent frozen embryo transfer (FET) cycles.

Pregancy follow-up

β-HCG was measured 2 weeks after embryo transfer, the number is 420pg/ml. Then at gestational week 7-9, fetal heart beating can be seen by ultrasonography. Luteal support was decreased untill 90 days, and her cabergoline dose was tapered from gestation month three until withdrawal. In August 2012, she delivered a baby girl at full term. The baby weighed 3.4 kg, with no maternal or newborn complications. She produced enough milk during breast-feeding, and her menstrual cycle resumed at month seven after birth. At the time, her menstrual cycle was 30 to 40 days, with moderate flow. The patient still had galactorrhea after the end of breast-feeding. She had a serum PRL test again at Octorber, 2016, and the PRL is 45ng/ml .She did not take other drugs after dopamine agonist withdrawal. She did not use any birth control methods nor did she become pregnant during the four-year follow-up period.

Newborn follow-up

The baby girl underwent normal development, and her height, weight, blood pressure, head circumference, and chest circumference were similar to those of other children her age. Her motor coordination and mental development were normal. Her social skills (per the Achenbach Child Behavior Checklist [CBCL] score) were similar to those of children of her age.

Discussion

We describe a very rare case of a 32-year-old woman with unexplained hyperprolactinemia, who following 1 year of almost complete anti-secretory response dopamine agonist therapy first with bromocriptine, developed secondary resistance to bromocriptine and cabergoline. This phenomenon has hitherto been described scarce.

PRL is secreted by prolactin cells in the anterior pituitary; however, recent studies have shown that PRL may also be secreted by other types of cells in the anterior pituitary [6]. PRL plays an important role during breast-feeding and pregnancy and is involved in certain physiological functions, such as angiogenesis, immune regulation, and osmotic regulation [7]. Under physiological conditions, PRL regulation is predominantly inhibitory, and any factor that interferes with hypothalamic dopamine synthesis and its transport to the pituitary or affects the interaction between dopamine and its receptors can weaken the inhibitory regulation, resulting in hyperprolactinemia. Common causes include physiological, pathological, pharmacological, and idiopathic factors. Idiopathic hyperprolactinemia is defined as high serum PRL (typically < 4.55 nmol/L), with negative examination results of the pituitary and central nervous systems and positive symptoms including galactorrhea, oligomenorrhea, and amenorrhea.

For the patient in this report, physiological factors were ruled out. Moreover, the patient had no history of long-term use of other drugs. Physical examination and laboratory testing ruled out obvious pathological changes, such as hypothalamic-pituitary diseases. Thus, the patient was diagnosed as having idiopathic hyperprolactinemia. However, most patients with idiopathic hyperprolactinemia have relatively low PRL levels, whereas this patient's baseline PRL was > 300 pg/mL; the chance of prolactinoma is greater if the PRL level is > 250 pg/mL [8]. For this patient, hyperprolactinemia might be related to micro-prolactinoma, which is undetectable with available diagnostic tools. Another potential factor is hypothalamic regulatory disorders [9].

Dopamine receptor agonists (such as cabergoline and bromocriptine) are current common, first-line treatments for hyperprolactinemia. Cabergoline is a relatively new specific dopamine D2 receptor agonist. Triantafilo *et al.* [10] conducted a meta-analysis and found that cabergoline is more effective for amenorrhea, irregular menstruation, and galactorrhea; improves pregnancy rates; and is more advantageous in patients unable to tolerate bromocriptine or who are resistant to bromocriptine.

The patient's medical records showed that her PRL level was still high after bromocriptine treatment (six tablets/day)after one-year treated with bromocriptine. She was then converted to cabergoline with a dose escalation to the maximum tolerated dose, but her PRL level remained high. According to the literature, dopamine agonist resistance is defined as higher than normal serum PRL and/or no tumor shrinkage after dopamine treatment. Up to 25% of patients fail to achieve normal PRL levels after bromocriptine treatment, and 10% to 15% of patients fail to have their PRL levels under control after cabergoline treatment. After bromocriptine treatment, 20% of patients with micro-prolactinoma and 30% of patients with macroprolactinoma continue to have high PRL levels, but cabergoline can increase the response rates by 10% and 20%, respectively, likely related to the higher affinity of cabergoline to dopamine-binding sites, the longer duration of binding, and the slower clearance [11]. Nevertheless, one study showed that two cabergoline-resistant prolactinoma patients achieved satisfactory treatment results after bromocriptine treatment [12].

Dopamine agonist resistance is uncommon in prolactinoma patients; cabergoline 2.0 mg/week is usually effective for controlling PRL secretion and reducing prolactinoma size [13]. Few patients who initially respond to dopamine agonists develop later resistance; to date, only five such cases have been reported, and the mechanism of secondary resistance is unknown [14]. In this report, the patient had

hyperprolactinemia, and her serum PRL level remained uncontrolled after one-year treated with bromocriptine. which can be diagnosised secondary resistance?

For patients with dopamine agonist resistantance, treatment options include conversion to other dopamine agonists and a dose increase to the maximum tolerated dose. For patients unable to tolerate oral bromocriptine, the drug may be given via the vagina. Ono et al [15] showed that among 60 treatment-naïve prolactinoma patients, 11 (18.3%) required a dose of > 2 mg/week cabergoline to achieve normal PRL levels (in one case, the dose even reached 11 mg/week). In this report, the patient's PRL level remained uncontrolled after conversion; it is unknown whether a higher cabergoline dose could achieve better results since the patient complained of severe adverse reactions if the cabergoline dose was greater than 3 mg/week. Therefore, further research is needed to investigate how to control hyperprolactinemia while mitigating adverse reactions.

In this report, the patient visited our hospitals mainly for infertility (caused by hyperprolactinemia). Numerous studies have shown that hyperprolactinemia is a common cause of anovulation, as hyperprolactinemia can act on the hypothalamus via short-loop feedback to stimulate dopamine secretion, which, in turn, inhibits GnRH, FSH, and LH secretion [16] and reduces kisspeptin expression [17], thereby inhibiting follicle development, maturation, and ovulation and inducing low egg quality, low fertilizing capability, division disorder, and infertility. Inhibition of LH secretion causes luteal degradation, luteal dysfunction, a high spontaneous abortion rate, and a high risk of infertility.

For patients who wish to become pregnant, ovulation induction therapy, such as clomiphene citrate and gonadotropin, may be given [18]. In this report, the patient received ovulation induction therapy. However, during treatment, it was noted that follicle development and ovulation occurred only during cycle one of either drug treatment. During clomiphene citrate treatment, dominant follicles luteinized during cycle two; during hMG treatment, no dominant follicle growth was observed during cycle two; during hMG treatment with a higher dose, follicles luteinized during cycles two and three. During IVF-ET, the embryo quality was not high, and the PRL level increased with E2. Follicular dysplasia may be related to mental stress and high PRL levels.

Studies have reached similar conclusions about the safety of cabergoline and bromocriptine in early pregnancy. To date, approximately 900 patients have taken cabergoline in early pregnancy, and safety evaluations of fetuses and newborns showed no significant increases in the early abortion, preterm birth, and multiple pregnancy rates or birth defects [19], which was consistent with the follow-up findings of this report. For this patient, after pregnancy was confirmed, the cabergoline dose was tapered until withdrawal. The baby girl was followed up for four years, and her height, weight, blood pressure, head circumference, and chest circumference were similar to those of children of the same age. Her motor coordination and mental development were normal, and her social skills (per CBCL score) were similar to those of children of the same age. For the patient, her menstrual cycle resumed at month seven after birth. At the time, her menstrual cycle was 30 to 40 days, with moderate flow. She still had galactorrhea after the end of breast-feeding. She did not take other drugs after dopamine agonist withdrawal. She did not use birth control methods nor did she become pregnant during the four-year follow-up period. She have a serum PRL test in 10, 2016 and the PRL is 45ng/ml. A 35-year follow-up study showed that for hyperprolactinemia patients, treatment was highly

effective in 20.8% (10/48) of the patients and effective in 68.8% (33/48) of the patients. Higher cabergoline doses were required in only 10.4% (5/48) of the patients due to increasing PRL levels [20]. Thus, highly effective treatment is available for hyperprolactinemia, but PRL levels should be monitored regularly, and hypothalamic-pituitary diseases must be ruled out in cases of increasing PRL levels.

Conclusion

We described a rare case of a 32-year-old woman with unexplained hyperprolactinemia who developed secondary dopamine agonist resistance following 1 years of DA therapy. As the underlying mechanism is unknown, patients who wish to become pregnant should be advised to reduce mental stress, and treatment may be given to reduce PRL levels to restore ovulation. Ovulation induction and assisted reproductive therapy may be given as necessary to facilitate pregnancy. Once the patient becomes pregnant, the dose of the dopamine agonist should be tapered as soon as possible to minimize its effect on the fetus.

Acknowledgements

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

LinlinLiang,Ph,D: Manuscript Drafting, Critical Discussion;

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All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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