Case Report

Acute intermittent porphyria exacerbation following in vitro fertilization treatment

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OBJECTIVE: Assisted reproductive technology is commonly used for women with infertility. We report a case of acute intermittent porphyria associated with in vitro fertilization treatment.

Case Report: A 35-year-old woman with tubal factor infertility presented to our clinic with persistent low abdominal pain and hyponatremia after transvaginal oocyte retrieval. During admission, she experienced a generalized tonic-clonic seizure attacked following by dark brown color urine. Urinary tests showed elevated porphobilinogen, 5-aminolevulinic acid, uroporphyrin, and coproporphyrin, confirming the diagnosis of acute intermittent porphyria. The patient's condition continued to improve after hemin treatment and rehabilitation.

Conclusion: Newly onset acute intermittent porphyria during the course of controlled ovarian hyperstimulation for in vitro fertilization is a rare but possible complication. Acute intermittent porphyria should be taken into consideration for persisted unexplained abdominal pain and seriously alerted if accompanied with neurological symptoms. Special tests for acute intermittent porphyria should be taken into consideration for the differential diagnosis of lower abdominal pain after oocyte retrieval.

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Introduction

Acute intermittent porphyria (AIP) is an autosomal dominant disorder with low penetrance resulting from a partial deficiency of the heme biosynthetic enzyme porphobilinogen deaminase [1]. Alterations in the enzymes of heme biosynthesis cause a variety of neurovisceral symptoms. The diagnosis of AIP should be considered in many patients with otherwise unexplained abdominal pain, severe constipation, systemic arterial hypertension, or other characteristic symptoms. It is a rare disease which affects reproductive age women more commonly than men. Development of symptoms is affected by a variety of exacerbating factors including sex hormones.

Oocyte retrieval in assisted reproductive technology is nowadays achieved almost exclusively by the transvaginal ultrasound-guided follicle aspiration method. Hormonal level fluctuations before and after oocytes retrieval could potentially induce exacerbations of AIP. We present a case of AIP exacerbations manifested as a rare complication which may be associated with hormonal fluctuation during in vitro fertilization (IVF) treatment.

Case Report

A 35-year-old nulliparous woman with a history of ectopic pregnancy came to our infertility department in hopes of pregnancy. Bilateral tubal occlusion was suspected under hysterosalpingography and IVF treatment was advised. The flare up protocol with gonadotropin-releasing hormone agonist (Leuprolide Acetate; FAMR L'Aigle, France) 1.0 mg per day was administered subcutaneously. Human chorionic gonadotropin (HCG) was given to trigger ovulation. The patient's estrogen level was 3650 pg/mL and progesterone level was 1.86 ng/mL on the day of HCG administration. Transvaginal oocyte retrieval (TVOR) was done smoothly 36 hours after the administration of HCG, with a total of
15 oocytes retrieved. Due to premature elevated progesterone level on the day of HCG, all fertilized embryos were cryopreserved.

The woman presented to the emergency department (ED) on the next day after the surgery with acute onset lower abdominal pain. Physical examinations showed lower abdominal tenderness and rebound tenderness. Small amount of ascites was noted under ultrasonography and post-TVOR peritonitis was suspected. Her symptoms improved gradually after the administration of intravenous fluid, oral antibiotics, and analgesics. She was then discharged from the ED after 57 hours of stay.

The patient presented to the ED again 4 days after TVOR. This time, she complained of right upper quadrant and lower abdominal pain. Nausea and vomiting were also found. Laboratory work-up was unremarkable except for hyponatremia (Na 127 mmol/L). Imaging studies with abdominal ultrasonography and computed tomography (CT) revealed enlarged bilateral adnexae with small amount of ascites. Early onset of ovarian hyperstimulation syndrome was suspected. Conservative management was taken. Her symptoms improved on the next day, and the patient was discharged again from the ED.

The patient visited our out-patient clinic 9 days after TVOR, complaining of persisted intermittent abdominal pain. She also asked for menstrual manipulation. Intramuscular injection with 50 mg progesterone was given in hopes of reducing the patient’s anxiety and discomfort. However, her symptoms persisted and reported again to our ED for the third time on the 11th day after TVOR. Right lower quadrant pain with abdominal fullness aggra- vated and no bowel movement for 4 days were complaints. Follow-up lab work-ups revealed persisted hyponatremia (Na 127 mg/dL). Plain abdominal film (Figure 1) showed distended colon and fecal impaction. Due to persisted abdominal pain, the patient was hospitalized on the 13th day after TVOR.

After admission, gastroenterologists were consulted and they suspected Ogilvie’s syndrome. Supportive care was suggested. For persistent hyponatremia, nephrologists suggested it might be related to syndrome of inappropriate antidiuretic hormone. How- ever, on the 2nd day of her admission, generalized tonic–clonic seizure occurred twice. Her seizures lasted for several minutes which ceased spontaneously before any intervention. Neurologists were consulted. Brain CT showed a hypodense lesion at the right parieto-occipital lobe. Abdominal CT revealed bilateral ovarian cysts and markedly dilated colon. Dilantin was given for 6 consecutive days as suggested by the neurologist, but another seizure episode occurred. Brain magnetic resonance imaging was performed and revealed amorphous lesions with hyperintensity on T2 weighted fluid-attenuated inversion recovery (T2 FLAIR) imaging (Figure 2) and hypointensity on diffuse weighted imaging in the bilateral parieto-occipital and right frontal lobes, suggesting poste- rior reversible encephalopathy syndrome. Also, dark brown color urine was found during hospitalization. Urinary tests showed
elevated porphobilinogen (PBG), 5-aminolevulinic acid, uroporphyrin, and coproporphyrins. The patient's serum examinations further showed a decrease in PBG deaminase level confirming the diagnosis of AIP.

The patient was transferred to the Neurology department under the diagnosis of AIP and hemin (Ever Pharma Jena Gmbh, Germany) was administered. The abdominal pain improved, but her neurological symptoms progressed to quadriplegia. After 2 weeks of treatment in the Neurology ward, the patient's condition improved slowly. She was sent to the rehabilitation department, and the neurological symptoms continued to improve after 6 months of rehabilitation. She regained most of her muscle power and was able to walk independently for a short distance.

Discussion

Alteration of the activities of enzymes in the biosynthetic pathway of heme can cause metabolic disorders known as porphyrias. According to the primary clinical presentations, porphyrias are classified as acute or cutaneous. AIP is the most common type of acute porphyria worldwide, with an estimated prevalence of approximately five per 1,000,000 [1]. Common neurovisceral manifestations for AIP include abdominal pain, gastrointestinal symptoms, muscle weakness and psychiatric symptoms [2], but the symptoms could be highly variable. Abdominal pain is the most common and often the earliest symptom of acute porphyria, affecting 85–95% of patients with AIP. The pain is neuropathic, and therefore usually unremitting and poorly localized [2]. Associated gastrointestinal symptoms including constipation, bloating, nausea, vomiting, and signs of ileus can be present at the same time. Inflammatory responses such as abdominal tenderness, rebound tenderness, fever, and leukocytosis are usually absent, but the presence of inflammatory signs cannot exclude the attack of AIP. As the AIP has a nonspecific and variable presentation, the diagnosis of AIP could easily be delayed. Identifiable exacerbating factors for AIP precipitating the onset of the disease are discussed in the literature [2–5]. Progesterone has been proposed as one of the exacerbating factors, supported by the evidence from clinical observations [6,7]. In our case, a relatively high progesterone level on the day of HCG administration, and an expected even higher level of progesterone after TVOR may be important factors for the exacerbation of the patient's AIP. Besides, the intramuscular progestin administered on the patient's follow-up visit may also contribute to the attack of AIP.

Ultrasound-guided TVOR was first described in 1985 [8]. By virtue of its simplicity, effectiveness and low rate of major complications, it is now performed routinely worldwide for oocyte pickup in IVF therapy. Nevertheless, despite its nature as a minimally invasive procedure, the aspiration needle may inadvertently

Figure 2. Brain MRI revealed amorphous lesions with hyperintensity on T2 FLAIR images in bilateral parieto-occipital and right frontal lobes. MRI – magnetic resonance imaging.
injure the adjacent pelvic structures and cause bleeding and trauma on surrounding organs. Trauma on the bowel during the TVOR remains a concern particularly when previous surgeries, pelvic infection, or endometriosis has caused extensive adhesion formation in the peritoneal cavity. However, in the literature, damage to the bowel appears to be rare [9–11]. Only two cases of perforated appendicitis following TVOR in which puncture holes were found in the appendix have been published [9, 11]. Ludwig et al [10] did a prospective study on > 1,000 oocyte retrievals and found no case of bowel injury, and the author suggested that the risk of damage to the bowel during an TVOR appears to be more theoretical than actual with the direct visualization of the peristaltic bowel. However, the author also proposed that bowel injuries might actually occur more frequently and cause minor symptoms without being diagnosed which resolve spontaneously [10]. Abdominal pain after TVOR is a relatively common nonspecific complaint. The symptoms of traumatized bowel include abdominal pain, nausea, signs of ileus, and decrease bowel sounds could mimic the acute attack of AIP, making early diagnosis of AIP after TVOR more difficult. As the diagnosis of AIP requires specific tests which are often not available in general medical facilities, it is time consuming to establish a confirmed diagnosis. High index of suspicion should therefore be taken if recurrent undiagnosed neurovisceral symptoms are found following IVF treatment.

Conclusion

Newly onset AIP during the course of IVF therapy is a rare but possible complication. AIP should be taken into consideration for those with persistent unexplained abdominal pain during controlled ovarian hyperstimulation, especially when accompanied with other neurological symptoms.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References