Cases of Persistant Hyperprolactinemia due to Prolactinoma according to DHPR and PTPS Deficiency

Hüseyin Kutay Körbeyli1, Mehmet Balci1,Meryem Karaca1,Arzu Selamioğlu1,Aslı Durmuş1, Mübeccel Demirkol1 and Gülden Gökçay1
1:İstanbul Faculty of Medicine, Division of Pediatric Nutrition and Metabolism

INTRODUCTION
Tetrahydrobiopterin (BH4) is a cofactor of phenylalanine hydroxylase (PAH), tyrosine-3 hydroxylase (TH), tryptophan-5 hydroxylase (TPH) and nitric oxide synthase (NOS) enzymes. TH and TPH enzymes are key enzymes in the synthesis of dopamine and serotonin. Regeneration and biosynthesis of BH4 are impaired in the defects of dihydropteridine reductase (DHPR) and 6-Pyruvyl tetrahydrobiopterin reductase (PTPS), respectively. L-Dopa Carbidopa combination and 5-hydroxytryptophan are used in the treatment of these defects. Routine prolactin (PRL) measurements are performed to monitor dopamine levels in the central nervous system. In this report, we present a case of DHPR deficiency diagnosed as prolactinoma due to high prolactin level detected in routine examinations, and a case of PTPS deficiency diagnosed as prolactinoma as a result of further examinations due to a pause in height growth.

CASES
CASE 1
A 21 years and 9 months old male patient diagnosed with DHPR, born from a first-degree cousin marriage, was taken to an external center with complaints of decreased breastfeeding duration, vomiting, and inability to gain weight in the neonatal period. He was referred to our center after his phenylalanine (phe) level was found to be 24 mg/dl. She was brought to our center on the postnatal 40th day.
Cerebrospinal fluid examination was performed with the prediagnosis of DHPR defect in the patient with a head circumference of 34 cm (< 3p) and 5 hydroxyindoleacetic acid: 0 nmol/l, homovanillic acid: 0 nmol/l, biopterin: 45 nmol/l (normal reference range: 15-40 nmol/l), neopterin: 23 nmol/l (normal reference range: 12-30 nmol/l) were found. The patient was followed up with the diagnosis of DHPR deficiency. L-Dopa-carbidopa combination, 5-hydroxytryptophan, folinic acid and phenylalanine restricted diet treatments were started. His neuromotor development was behind his chronological age during the whole follow-up period. Phenobarbital treatment was performed at the age of 5 months due to hypertonicity. The central nervous system dopamine levels of the patient were monitored with routine prolactin measurements. When the patient was 19 years old, the studied prolactin level was found to be 1522 ng/ml (normal reference range <25 ng/ml). Cranial MRI revealed a 14x12x9 mm macroadenoma in the adenohypophysis. The patient was consulted to the endocrinology department, cabergoline treatment was started, and a dramatic decrease in prolactin levels was observed.

CASE-2

A 14-year-old, 11-month-old female patient diagnosed with PTPS defect, born to unrelated parents, was referred to our hospital because the Phe level was found to be 26 mg/dl in the postnatal 3rd month screening test. The patient was followed up in the prenatal period due to oligohydramnios and was born at the 38th week of gestation with a weight of 21500 g. She was followed in the neonatal intensive care unit due to being small for gestational age (SGA), transient tachypnea of the newborn, and meconium ileus, and cystic fibrosis was ruled out. The patient was 3 months old when he first came to our hospital, and during this period, pterin levels and DHPR activity in dried blood spots were analyzed. Erythrocyte DHPR activity: 3.2 mU/mg Hb (normal reference range: 1.8 - 4.8 mU/mg Hb), neopterin: 22.21 nmol/l (normal reference range: 3 - 11 nmol/l), biopterin: 0 nmol/l (normal reference range: 4 - 11 nmol/l) and the patient was started to be followed up with a preliminary diagnosis of PTPS defect. L-Dopa-carbidopa combination, 5-hydroxytryptophan and cofactor BH4 treatments were started.
Cerebrospinal fluid analysis was performed when the patient was 11 months old, 5-hydroxyindolacetic acid: 78.2 nmol/l (normal reference range: 114-336 nmol/l), homovalinic acid: 79.8 nmol/l (normal reference range: 295-932 nmol/l), neopterin: 200nmol/l (normal reference range: 12-30 nmol/l), biopterin: 4.8 nmol/l (normal reference range: 15-40 nmol/l). The patient was neuromotor retarded and microcephalic during the follow-up period. Since the patient stopped growing in height at the age of 12, he was referred to the pediatric endocrinologist, and a 13x8.5 mm macroadenoma was found in the center of the hypophysis gland in his cranial MRI. Cabergoline was started because the localization of the mass was not suitable for surgery.

DISCUSSION

In the cases presented in this report, two cases that developed prolactinoma while being followed up due to cofactor BH4 metabolism defect are discussed. We want to contribute to the literature by presenting these cases. More studies are needed to explain the pathophysiology of the relationship between BH4 metabolic disorders and prolactinoma.

Image-1: In the pituitary MRI of Case 1, macroadamia is observed in the postcontrast coronal section.
Image 2: Macroadenoma in sagittal section on postcontrast MRI of Case - 1

Image 3: In case 1, postcontrast MRI performed after cabergoline treatment showed regression in the lesion.
Image- 4: Macroadenoma is seen in the postcontrast cranial MRI of Case 2.

Image-5: Postcontrast cranial MRI after cabergoline treatment of Case2 shows regression in the lesion.