

# Pituitary Apoplexy Due to Thyroxine Therapy in a Patient with Congenital Hypothyroidism

**Murat Tutanc<sup>1</sup>, Murat Altas<sup>2</sup>, Erhan Yengil<sup>3</sup>, Ihsan Ustun<sup>4</sup>,  
Kenan S. Dolapcioglu<sup>5</sup>, Ali Balci<sup>6</sup>, Fatih Sefil<sup>7</sup>, Cumali Gokce<sup>4</sup>**

<sup>1</sup> Department of Pediatric, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey.

<sup>2</sup> Department of Neurosurgery, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey.

<sup>3</sup> Department of Family Medicine, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey.

<sup>4</sup> Department of Endocrinology and Metabolism, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey.

<sup>5</sup> Department of Obstetrics and Gynecology, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey.

<sup>6</sup> Department of Radiology, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey.

<sup>7</sup> Department of Fیزیology, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey.

## Correspondence mail:

Cumali Gokce, MD, Assoc. Prof., Department of Endocrinology and Metabolism, Faculty of Medicine, Mustafa Kemal University. 31100 Hatay, TURKEY. Email: cumaligokce@yahoo.com, dryengil@yahoo.com.

## ABSTRAK

Seorang wanita berusia 24 tahun masuk rumah sakit dengan keluhan kelemahan, pembengkakan umbilikus, keterlambatan perkembangan, gangguan bicara, konstipasi, dan kelainan gaya berjalan. Pada pemeriksaan ditemukan hernia umbilikus, xerosis, rambut kering dan perawakan pendek. Setelah dilakukan pengobatan dengan tiroksin, ia juga mengalami sakit kepala, muntah dan palpitasi, kurang nafsu makan serta gangguan tidur. Pencitraan magnetic resonance imaging (MRI) kelenjar hipofisis menunjukkan adanya massa heterogen di bagian pusat kelenjar pada potongan koronal dan diinterpretasikan sebagai apopleksia hipofisis (pituitary apoplexy). Pada kasus ini, pasien dengan hipotiroidisme kongenital atau congenital hypothyroidism (CH) ternyata mengalami apopleksia hipofisis atau pituitary apoplexy (PA) pasca terapi tiroksin. Oleh karena itu, keluhan agaknya lebih berhubungan dengan PA daripada insufisiensi adrenal. Pada artikel ini, kami menyajikan sebuah laporan kasus yang mengevaluasi PA pada seorang pasien dengan adenoma hipofisis tirotropik yang disebabkan oleh CH. Sepanjang pengetahuan kami, ini adalah kasus pertama PA yang berkaitan dengan CH pasca terapi tiroksin dalam kepustakaan.

**Kata kunci:** hipotiroidisme kongenital, apopleksia hipofisis, terapi tiroksin.

## ABSTRACT

A 24-year-old woman was admitted with general weakness, umbilical swelling, developmental delay, speech disorder, constipation, gait problem. Her findings were umbilical hernia, xerosis, dry hair, and short stature. After thyroxine treatment, she also had headache, vomiting, and palpitation, lack of appetite, and sleep disturbance. Pituitary magnetic resonance imaging revealed a heterogeneous mass at the central part of the gland on coronal section and it was interpreted as pituitary apoplexy. In the current case, the patient with congenital hypothyroidism (CH) developed pituitary apoplexy (PA) after thyroxine therapy. Therefore, it is suggested that the complaints were related to PA rather than adrenal insufficiency. Here we describe a case report evaluating PA in a patient with thyrotrophic pituitary adenoma due to CH. To the best of our knowledge, this is the first case in terms of PA associated with CH after thyroxine therapy in the literature.

**Key words:** congenital hypothyroidism, pituitary apoplexy, thyroxine therapy.

## INTRODUCTION

Congenital hypothyroidism (CH) is usually caused by the dysgenesis of thyroid gland, and it is one of the common and preventable causes of mental retardation. CH is characterized by dwarfism, mental retardation, decreased physical activity, short stature or growth retardation, constipation, macroglossia, umbilical hernia, cool and dry skin, myxedema and anemia.<sup>1,2</sup> Also, it is one of the most frequent causes of growth and developmental delays and preventable mental retardation in children.<sup>3</sup>

Hypophyseal adenomas (HA) are the 10-20 percent of all the intracranial tumors and commonly seen between 3 and 6 decades.<sup>4</sup> They are very rare in children and have the same prevalence in males and females. HA are classified as in related to secreted hormones: Prolactin, GH, ACTH, FSH-LH, TSH secreting and non-secreting adenomas.<sup>4,5</sup> HA secondary to CH is a common etiology of pituitary enlargement and most of thyrotroph adenomas due to CH.<sup>6</sup> Secondary pituitary enlargement in adults and children can be seen in patients with acquired and CH. HA in patients with long standing hypothyroidism is rare. There are only few reports evaluating secondary adenoma due to CH as primarily underlying disease.<sup>7,8</sup>

Pituitary apoplexy (PA) is very serious and hazardous disorder, but it is not common.<sup>9,10</sup> PA is a medical emergency due to acute infarction or hemorrhage in the pituitary gland.<sup>11</sup> Most of the cases occur spontaneously in patients with untreated pituitary adenomas (PADs), but it may also occur after a number of events such as pituitary stimulation tests,<sup>11-17</sup> drug therapy.<sup>18,19</sup> Common clinical findings of this disorder are headache, nausea, vomiting, visual impairment, altered mental status, and even coma.<sup>10,11,17</sup> Treatment of PA in the acute stage is still controversial in terms of surgical intervention. Regardless the severity of clinical presentation, the course of PA is unpredictable. The choice for conservative or surgical management is generally individual.<sup>11</sup>

Here we describe a case report investigating PA in a 24-year-old female patient with thyrotrophic PAD due to CH. When thyroxine therapy was started in a state hospital, her complaints were

weakness, umbilical swelling, developmental delay, speech disorder, constipation, gait problem, and her findings were umbilical hernia, xerosis, dry hair, and short stature. After the treatment, she also had headache, vomiting, palpitation, lack of appetite, and sleep disturbance. Pituitary magnetic resonance imaging (MRI) revealed a heterogeneous mass at the central part of the gland on coronal section and it was interpreted as pituitary apoplexy. To the best of our knowledge, this is the first case in terms of PA associated with CH after thyroxine therapy in the literature.

## CASE ILLUSTRATION

A 24-year-old (bone age: 8 years old) female patient was referred to the University Hospital due to the management of developmental delay and the other complaints in March 2010 (**Figure 1**). Ten days before, she had admitted to the Outpatient Clinic of a state hospital because of the same complaints and thyroxine therapy was given for the diagnosis of CH. When the drug therapy was started, her complaints were weakness, umbilical swelling, developmental delay, speech disorder, gait problem, constipation and her findings were short stature, low weight and height (the height was 109 cm, and the weight was 28 kg; they are below the 5th percentile of the standards), Tanner Stage 3 breast development, umbilical hernia, xerosis, and dry hair. After thyroxine treatment, she also had headache, vomiting, palpitation, lack of appetite, and sleep disturbance. When the case was ten years old, she started to talk and her speech was better and learnt the colors and



**Figure 1.** The patient had delayed somatic and sexual development. In addition to flattened nasal root, dry hair, low ear line.

numbers. According to the parents' history, she was initially hospitalized at a state hospital for gait and speech disorder 17 years ago (7-year-old). The case had been diagnosed as CH and had had a drug therapy. However, the therapy had been stopped by her parents after a few months without informing the doctor. The patient and her family are still living at the rural area of Hatay which is a city located at the southern part of Turkey. The family came from low economical status and level of education.

Ten days later, the patient was admitted to the Outpatient Clinic of Endocrinology and Metabolism, and she was hospitalized at the clinic in March 2010. After the drug treatment, in addition to initial complaints, she also had headache, vomiting, palpitation, lack of appetite, and sleep disturbance. On physical and psychiatric examination, she had mental retardation, dry hair, flattened nasal root, macroglossia, umbilical hernia, and dry skin regarding CH. Her pulse and blood pressure were in normal limits (pulse: 72 per minute, blood pressure: 100/60 mm/Hg). The height and weight were below the 5th percentile of the standards.

After clinical and laboratory assessment, it was revealed that the patient had anemia, CH, GH deficiency, and secondary adrenal insufficiency. Thyroid ultrasonography showed an atrophic gland. On the hand-wrist graphy, the bone age was consistent with 8 years old regarding developmental delay due to CH (**Figure 2**). Pituitary MRI showed a heterogeneous mass at the central part of the gland on coronal plan (**Figure 3**).

Severe mental retardation was detected at the patient's psychiatric examination (MA) after some intelligence quality tests. The patient also had dysfunctional uterine bleeding, and endometrial hyperplasia assessed by gynecologist (KSD). A progestin containing oral contraceptive was given. The case was also consulted by the neurosurgeon (MA) in aspect of PA. Conservative management was recommended.

Firstly, thyroxine was stopped. After the detailed investigation in aspect of biochemical, hormonal, imaging, and dynamic tests, glucocorticoid replacement therapy was started.



**Figure 2.** Osteoporosis and delayed bone age on hand wrist graphy



**Figure 3.** Coronal MRI section of the pituitary gland displaying a heterogeneous mass

## DISCUSSION

CH is characterized by dwarfism, large fontanels, mental retardation, decreased physical activity, poor feeding and weight gain, small stature or poor growth, a distended abdomen, decreased stooling, constipation, macroglossia, umbilical hernia, cool and dry skin, developmental delay, pallor, myxedema, and anemia.<sup>1,2</sup> Also, it is one of the most frequent causes of preventable growth and developmental delays and mental retardation in children.<sup>3</sup> In the present case, the findings on physical examination were mental retardation, sexual and somatic retardation, flattened nasal root, macroglossia, umbilical hernia, cool and dry skin and hair. Laboratory parameters revealed hypopituitarism including low T3 and T4, low GH, low gonadotrophin hormones and high TSH levels related to CH. Thyroid ultrasonography displayed the gland

atrophy regarding CH.<sup>2</sup>

PADs are very rare in children classified in related to secreted hormones: prolactin, GH, ACTH, FSH-LH, TSH secreting and non-secreting adenomas.<sup>3-5</sup> TSH adenomas may cause inappropriate TSH syndrome and hyperthyroidism.<sup>20</sup> HA secondary to primary hypothyroidism (PH) is a common etiology of pituitary enlargement and most of adenomas due to PH.<sup>6</sup> Secondary pituitary enlargement in adults and children can be seen in patients with acquired and congenital hypothyroidism. PADs in patients with long standing hypothyroidism are very rare. There are only few reports evaluating secondary adenoma due to CH as primarily underlying disease.<sup>7,8</sup> It was due to inadequate treatment, and their patients had long-standing history.<sup>7</sup> The patient's laboratory findings were consistent with hypothyroidism (low T4, high TSH) as in our case. The present case had also long-standing history and inadequate or no therapy.

PA is uncommon, although most serious and hazardous in patients with PADs.<sup>13,17</sup> The often underlying etiology related to PA (25% of cases) is pituitary stimulation tests<sup>11-17,21</sup> medication (cabergoline, gosereline, and bromocriptine)<sup>18,19,22</sup>, radiotherapy, trauma, thrombocytopenia or recent surgery.<sup>10</sup> Balarini et al.<sup>18</sup> and Knoepfelmacher et al.<sup>23</sup> reported that a patient with macroprolactinoma had PA during cabergoline therapy. In another study, Blaut et al.<sup>19</sup> revealed that a case with prostate carcinoma had PA during gosereline (LHRH analogue) therapy. In the other study, Singh et al.<sup>22</sup> reported a patient who had PA after bromocriptine therapy. In all the studies, the cases had headache, nausea, vomiting and visual abnormalities, and their pituitary MRI were consistent with PA as in our case.<sup>18,19,22,23</sup> However, in some reports, the laboratory parameters of the patients were in normal range in terms of hormonal and biochemical tests.<sup>18,19</sup> In the current case, the patient with CH developed PA after thyroxine therapy. The case had headache, vomiting, palpitation, lack of appetite, and sleep disturbance. Therefore, it is suggested that the complaints were related to PA rather than adrenal insufficiency as in the first case in the literature.

Most of the cases occur spontaneously in patients with untreated PAD, but it may also occur after a number of events such as dynamic tests.<sup>14</sup> PA due to the stimulation tests is commonly seen in patients with non-functioning and prolactin secreting adenomas.<sup>11-17,21</sup> The most common stimulants causing PA in cases with PAD are GnRH, TRH, and insulin, respectively. It was reported that a patient with acromegaly had PA due to GnRH and TRH stimulation tests. Therefore, the case was operated by transsphenoidal approach.<sup>5,16</sup> It is well known that PADs consisting of prolactin and GH are very susceptible to PA during dynamic tests and drug therapy. However, in the current report, there is a patient with PAD due to CH, and she had PA after therapy. On the other hand, in another paper, Atmaca et al. proposed that TRH stimulation test is necessary even if it may cause PA.<sup>24</sup>

Common clinical findings of the disorder are headache, nausea, vomiting, visual impairment, altered mental status, and even coma.<sup>10,25,26</sup> Some of them, such as headache, nausea, vomiting was existed in our patient. In addition, she had palpitation, lack of appetite, and sleep disturbance. In the current report, the patient had the complaints after thyroxine therapy before dynamic tests. Therefore, it is suggested that PA may be due to the drug therapy. Also, the peak cortisol response to insulin hypoglycemia test is close to the normal response as 17 ug/dl and the vital signs and electrolytes (especially potassium) are not consistent with adrenal insufficiency. All these findings seem to be related to PA rather than adrenal insufficiency. However, Balarini et al. reported that a patient with macroprolactinoma had PA during cabergoline therapy.<sup>18</sup> In this article, the patient has both PA and adrenal insufficiency and the case's hormones and electrolytes are consistent with adrenal insufficiency.

The differential diagnosis for PA includes subarachnoid hemorrhage due to ruptured intracranial aneurism, meningitis, basilar artery occlusion, hypertensive encephalopathy, brain abscess or cyst, cavernous sinus thrombosis, intracerebral hematoma, encephalitis, retro bulbar neuritis, temporal arteritis, and ophthalmologic

migraine. MRI frequently shows hyperdens lesions together with hypodens lesions.<sup>10,11</sup> Similar images were found in pituitary MRI of current case (**Figure 3**). Therefore, MRI and computerized tomography were carried out for the differential diagnosis in aspect of PA.

Management of PA in the acute phase is still controversial in terms of surgical treatment. Regardless the severity of clinical presentation the course of PA is unpredictable. The choice for conservative or surgical interventions is generally individually.<sup>13</sup> Untreated patients with apoplexy have higher morbidity and mortality. It should be kept in mind that if a patient with PA has both hypothyroidism and adrenal insufficiency, adrenal failure should be treated first and then thyroid hormone replacement should be given.<sup>25,26</sup>

## CONCLUSION

Here we describe a case report evaluating PA in a patient with thyrotrophic PADs due to CH. When thyroxine therapy was started in a state hospital, her complaints were weakness, umbilical swelling, developmental delay, speech disorder, constipation, gait problem, and her findings were umbilical hernia, xerosis, dry hair, and short stature. After the treatment, she also had headache, vomiting, and palpitation, lack of appetite, and sleep disturbance. Pituitary MRI revealed a heterogeneous mass at the central part of the gland on coronal section and it was interpreted as pituitary apoplexy. In the current case, the patient with CH developed PA after thyroxine therapy. The patient had headache, vomiting, and palpitation, lack of appetite, and sleep disturbance. Therefore, it is suggested that the complaints were related to PA rather than adrenal insufficiency. It should be kept in mind that if a patient with PA has both hypothyroidism and adrenal insufficiency, adrenal failure should be treated first and then thyroid hormone replacement should be given. To the best of our knowledge, this is the first case in terms of PA associated with CH after thyroxine therapy in the literature.

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