DOI: 10.4274/tjem.2754

Parathyroid Adenoma Complicated with Severe Hypercalcemia, Encephalopathy and Pancreatitis

Ciddi Hiperkalsemi, Ensefalopati ve Pankreatit ile Komplike Olmuş Paratiroid Adenomu

Pembe Okaygün, Hasan Sav*, Umut Mousa*, Varol Esatoğlu**, Turgut Küçük**, Osman Köseoğluları*, Sonuç Büyük***

Dr. Burhan Nalbantoğlu Hospital, Clinic of Internal Medicine, Lefkoşa, Cyprus
*Dr. Burhan Nalbantoğlu Hospital, Clinic of Endocrinology and Metabolism, Lefkoşa, Cyprus
**Dr. Burhan Nalbantoğlu Hospital, Clinic of General Surgery, Lefkoşa, Cyprus
***Dr. Burhan Nalbantoğlu Hospital, Clinic of Pathology, Lefkoşa, Cyprus

Abstract

Primary hyperparathyroidism is the most frequent cause of hypercalcemia in adults. Primary hyperparathyroidism generally leads to mild-moderate hypercalcemia. Severe hypercalcemia in these cases is rare. Coexistence of severe hypercalcemia and hypercalcemic encephalopathy is very unusual with very limited number of reported cases. Our case is a 50-year-old female who presented to the emergency department with the complaints of nausea and severe abdominal pain. Her serum calcium level was 19.7 mg/dL (8.8-10.2 mg/dL) and her PTH level was 73.5 ng/dL (15-65) on presentation. After her hospitalization, she was treated with saline infusions and furosemide, however, her calcium level increased to 22.4 mg/dL. Her calcium levels were also refractory to subcutaneous calcitonin 200 mg twice a day and zoledronic acid 4 mg. Ultrasonography of the neck revealed a 3.2x2.7x4.6 cm mass suspicious for a left parathyroid adenoma hardly being distinguished from a left thyroid nodule. Considering her general situation getting worse despite maximum medical treatment, she underwent an emergency parathyroidectomy and total thyroidectomy. Early postoperatively, the patient's general condition deteriorated reaching a precoma state. Cranial computed tomography (CT) at this point revealed periventricular ischemia compatible with metabolic encephalopathy. During the follow-up postoperatively, the patient's serum calcium levels normalized eventually requiring active vitamin D and calcium pills and she no longer had symptoms of encephalopathy. The pathology specimen was reported as a parathyroid neoplasm compatible with atypical parathyroid adenoma. Although mild-moderate hypercalcemia is frequent in primary hyperparathyroidism, it should be noted that it can be severe and refractory to maximum medical treatment requiring emergency surgical intervention. In addition, not being one of the most frequent reasons, severe hypercalcemia due to primary hyperparathyroidism should be considered as an important cause of metabolic encephalopathy. *Turk Jem 2015; 19: 105-108*

Key words: Hypercalcemia, encephalopathy, primary hyperparathyroidism

Özet

Erişkinlerde hiperkalseminin en sık görülen sebebi primer hiperparatiroididir. Primer hiperparatiroidinin yol açtığı kalsiyum yüksekliği genellikle ılımlıdır. Bu olgularda ciddi hiperkalsemi seyrektir. Bu olgularda ciddi hiperkalsemi ile birlikte hiperkalsemik ensefalopati birlikteliği seyrek görülmekte olup sınırlı sayıda olgu sunumu literatürde bildirilmiştir. Elli yaşındaki kadın olgumuz bulantı ve ciddi karın ağrısı şikayeti ile acil servise başvurusunda serum kalsiyum düzeyi 19,7 mg/dL (8,8-10,2 mg/dL) ve serum PTH düzeyi 73,5 (13-65) ng/dL olarak saptandı. Hastaneye yatışının ardından serum fizyolojik infüzyonu ve furosemid tedavisine rağmen kalsiyum düzeyi 22,4 mg/dL'ye kadar yükseldi. Kalsitonin günde 2 kez 200 mg subkutan ve zoledronik asit 4 mg intravenöz verilmesi sonrası da yanıt alınamadı. Boyun ultrasonografisinde sol lob inferiorunda tiroid nodülünden zor ayrılabilen ve paratiroid ile uyumlu olabilecek 3,2x2,7x4,6 cm kitle izlendi. Genel durumunun tedaviye rağmen bozulması üzerine acil total tiroidektomi ve sol paratiroidektomi operasyonuna alındı. Erken post op dönemde iyice genel durumu bozulan hastada bu aşamada pre koma hali mevcut olup çekin kranial BT metabolik ensefalopati ile uyumlu olan periventriküler iskemi olarak raporlandı. Post op takibinde serum kalsiyum düzeyleri tedricen düşen hastanın zaman içerisinde hipokalsemik seyretmesi üzerine aktif vitamin D ve kalsiyum preparatı tedaviye eklendi. Ensefalopati bulguları tamamen kayboldu. Bu esnada raporlanan patoloji incelemesi paratiroid adenomu ile uyumlu saptandı. Primer hiperparatiroidi olgularında genellikle ılımlı hiperkalsemi görülmesine rağmen bazen acil cerrahi girişim gerektiren malign hiperkalsemiye de yol açabileceği bu olgu sunumunda görülmüştür. Primer hiperparatiroidine bağlı hiperkalsemi ayrıca metabolik ensefalopatinin önemli sebeplerinden bir tanesidir. *Turk Jem 2015; 19: 105-108*

Anahtar kelimeler: Hiperkalsemi, ensefalopati, primer hiperparatiroidi

Address for Correspondence: Umut Mousa MD, Dr. Burhan Nalbantoğlu Hospital, Clinic of Endocrinology and Metabolism, Lefkoşa, Cyprus
E-mail: umutmousa@yahoo.co.uk **Received:** 25/08/2014 **Accepted:** 05/12/2014

Turkish Journal of Endocrinology and Metabolism, published by Galenos Publishing.

Introduction

Primary hyperparathyroidism (PHP) is a generalized disorder resulting from excessive secretion of parathyroid hormone (PTH) by one or more of the parathyroid glands (1). Solitary parathyroid adenomas represent approximately up to 85% to 90% of cases with PHP (2,3). The majority of the remainder is either parathyroid hyperplasia or multiple parathyroid adenomas (4,5). Parathyroid carcinoma rarely occurs and is responsible for only 0.7% of all cases (3). With increased detection by means of routine calcium screening, the clinical profile of PHP in Western countries has shifted from a symptomatic disease, characterized by hypercalcemic symptoms; nephrolithiasis, overt bone disease, and neuromuscular symptoms to one with subtle or no specific symptoms (asymptomatic primary hyperparathyroidism). In the developing world, the symptomatic variant still dominates (6).

In this report, we present a case of PHP presenting and progressing with severe neurological symptoms together with acute pancreatitis.

Case Report

A 50-year-old female was admitted to the emergency department with the complaints of severe abdominal pain and nausea lasting several weeks which recently increased in intensity. She mentioned hospital admission with similar complaints eleven years ago when she underwent cholecystectomy. She had no recent history of drug use and no history of chronic diseases. She recalls her laboratory tests being completely normal eleven years ago at the time of her cholecystectomy, but the laboratory report was unavailable at present time. On her admission to our hospital, she had abdominal tenderness on palpation and leucocytosis, hypercalcemia and elevated serum amylase levels (Table 1). She was then hospitalized at the department of general surgery with a prediagnosis of acute pancreatitis.

Intravenous hydration and antibiotics were initiated. The PTH level was 73.5 ng/dL (15-65) (Electrochemiluminescence immunoassay), thus, a neck ultrasonography (USG) was performed. The neck USG revealed a 3.2x2.7x4.6 cm homogenous, hyperechoic mass suspicious for a parathyroid adenoma hardly being distinguished from a the left thyroid nodule. Despite maximum medical therapy, consisting of intravenous hydration, furosemide, calcitonin and zoledronic acid, the serum calcium level increased to 22.9 mg/dL. Thyroid function tests were normal.

In less than a 24-hour period, her calcium level reached 24 mg/dL and her clinical condition deteriorated reaching a precoma state. Considering her general condition and severe hypercalcemia, emergent surgical intervention was planned with the prediagnosis of malignant hypercalcemia, hypercalcemic encephalopathy and PHP with the suspicion of parathyroid carcinoma as the cause of malignant hypercalcemia. Total thyroidectomy and left parathyroidectomy were performed.

Early after the operation, the calcium levels were still above 24 mmol/L. In addition, the patient's general condition got even worse; confusion and loss of cooperation continued. The cranial computed tomography scan at this point revealed periventricular ischemia which was compatible with metabolic encephalopathy due to hypercalcemia.

On the third day, the renal function tests and calcium levels improved. Her neurological symptoms no longer existed. Eventually, her serum calcium levels decreased to 8.1 mg/dL requiring oral calcium and active vitamin D supplementation.

The pathology report described parathyroid neoplasm compatible with atypical parathyroid adenoma because of its cellularity and some atypical features of the cells. No necrosis, atypical mitosis and capsular invasion were present. The Ki-67 proliferative index was 2%. Neoplastic cells stained positive with chromogranin (Figures 1, 2, 3).

Table 1. Significant laboratory tests on presentation. Normal range for each entity is expressed in parenthesis

White Blood Cells	13000 /mm^3 (4-10000)
Serum Calcium	19.7 mg/dL (8.8-10.2)
Serum Sodium	136 mEq/Lt (135-145)
Serum Potassium	2.8 mmol/L (3.5-5.1)
Serum Albumin	3.7 g/dL (3.5-5.0)
Serum Amylase	361 U/L (25-125)
Serum Phosphorus	2.4 mg/dL (2.3-4.7)
Serum Creatinine	0.9 mg/dL (0.6-1.1)
Serum Blood Urea Nitrogen (BUN)	22 mg/dL (10-20)
Alkaline Phosphotase (ALP)	120 IU/L (44-147)
Alanine Transaminase (ALT)	30 IU/L (10-40)

Discussion

The incidence of pancreatitis in hyperparathyroidism is controversial (7,8). Recent studies have stated that hyperparathyroidism is rarely associated with pancreatitis (1-7% of cases), but when such a combination does occur, pancreatitis is severe (9).

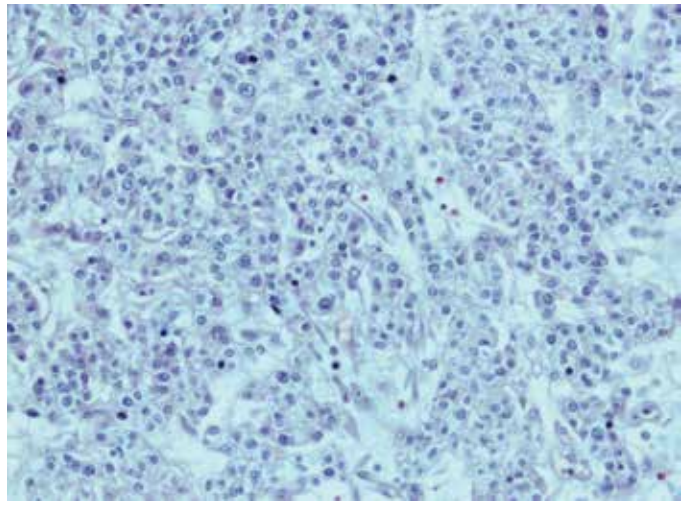

Figure 1. HE stain x 400

The pathogenesis of pancreatitis in the course of hyperparathyroidism is not well defined. Hyperparathyroidism is believed to cause pancreatitis by several mechanisms, the most common of which is hypercalcemia. The other hypercalcemic states, such as malignant diseases, vitamin D intoxication, hyperthyroidism, excessive calcium intake and parenteral nutrition, may also result in pancreatitis (10).

Animal studies have suggested that long-standing hypercalcemia directly affects pancreatic functions. According to some researchers, hypercalcemia secondary to hyperparathyroidism causes decreased pancreatic volume whereas pancreatic enzyme activity is not affected. These findings suggest that hypercalcemia may have some influence on exocrine pancreatic function (11). Persistent hypercalcemia may also result in an increased calcium concentration in pancreatic juice, and activate pancreatic trypsinogen to trypsin resulting in pancreatic ductal and parenchymal damage and pancreatitis (7,8,12). Long-standing hypercalcemia may also decrease the volume of pancreatic secretions leading to protein plugs in the pancreatic duct eventually obstructing the pancreatic flow leading to pancreatic inflammation (13).

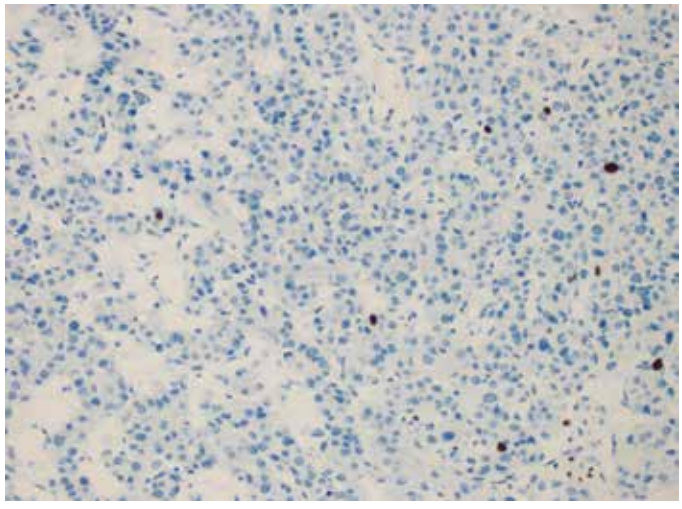

Figure 2. Ki-67 Stain x 100: 2% of cells stain positive

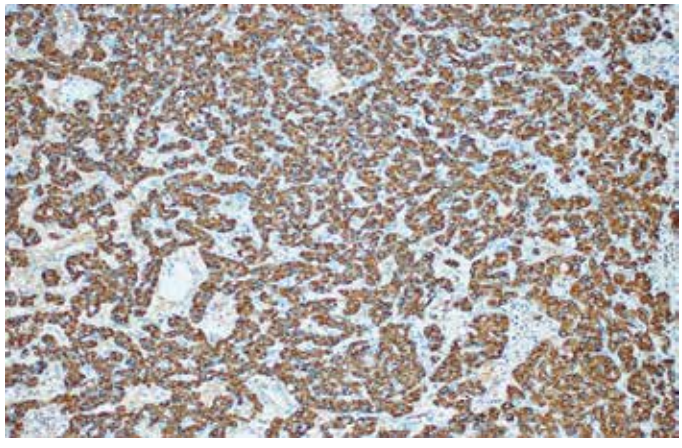

Figure 3. Chromogranine stain x 100: Cells stain positive for chromogranine

On the other hand, PTH itself has been suggested to be a cause of pancreatitis. The hormone may inhibit pancreatic blood circulation directly or by means of pancreatic ductal and blood vessel narrowing mediated by hypercalcemia. Some authors have also indicated that PTH itself may act as a toxin causing local thromboendarteritis and necrosis of pancreatic tissue (7,8). Micro embolisms due to hyperparathyroidism have also been reported. All of which may result in pancreatic tissue necrosis (7).

PHP and acute pancreatitis are rarely expected to co-exist (9). In our case, acute pancreatitis was the presenting feature.

Hypercalcemic crisis is an infrequent manifestation of PHP which calls for urgent surgical attention. The published reports of such cases clearly indicate that the syndrome of hypercalcemic crisis occurring in the course of PHP is almost uniformly fatal unless recognized early and the hyper functioning parathyroid tissue is promptly removed (14).

Central nervous system symptoms can vary from tiredness, headache to depression and even loss of initiative (15). According to an article that was presented at the 67th Annual Meeting of the Central Surgical Association in 2010, subjects with hypercalcemic crisis had a greater incidence of mental status changes, fatigue, ectopic glands, and pancreatitis (16).

In this case we studied, the increase in serum calcium level correlated with acute psychomotor deterioration and alteration in the level of consciousness. This finding was attributed to metabolic encephalopathy secondary to hypercalcemic crisis.

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological entity which has been described since the mid-90's (17). It is characterized by an acute alteration in the level of consciousness frequently accompanied by headache, seizures and focal neurological signs such as visual field defects (18).

This syndrome has been described in a wide variety of settings, most commonly, solid organ transplantation, hypertensive crisis, and immunosuppressive drug administration (18). In the literature, 8 cases of hypercalcemia related to PRES have been reported (19,20), only 2 of which were due to parathyroid adenomas (21,22). Since then, a case report by Giani et al., announced a new case of PRES in association with parathyroid adenoma (23).

The physiopathological mechanisms of PRES are still debated (18). There have been two main theories suggested to explain the condition. The first theory focuses on severe hypertension as the triggering condition of overflow edema, by disturbance in autoregulatory mechanism of the cerebral blood vessels. A second theory emphasizes the importance of altered blood brain barrier function resulting from a combination of endothelial dysfunction, hypoperfusion and vasoconstriction (24). Hypercalcemia and elevated PTH levels have been shown to induce the production of vascular endothelial growth factor (VEGF) and nitric oxide (NO) by way of which they can alter vascular permeability (25,26,27) as mentioned in the second theory.

In PRES, symptoms develop sub-acutely or acutely, often with seizures at onset (24). Imaging studies (both CT and magnetic resonance imaging) demonstrate focal regions of symmetric hemispheric edema in the brain (28,29) which usually reverses

completely (30) with early identification of the underlying etiology and its effective treatment (31).

Neurological symptoms that developed during the follow-up complicated the case. Considering severe hypercalcemia irresponsive to medical therapy and the neurological symptoms accompanying, two main entities were suspected: hypercalcemic crisis and PRES. The level of consciousness deteriorated progressively and acutely in correlation with progressively increasing levels of calcium and only moderately high PTH levels. This dramatically worsening of the patient's general condition made emergent surgical intervention inevitable. The underlying etiology of severe hypercalcemia was established to be a parathyroid adenoma. Furthermore, the progression of the case and acute regression after surgery, strongly suggested PRES. Due to the necessity of emergent surgery, radiological imaging studies could not be performed before surgery.

Generally, PTH levels are frankly elevated in cases with PHP, but in our case it was mildly elevated despite marked calcium elevation. This was unexpected, but in a study that compared patients with PHP having normal PTH levels with those having elevated PTH levels, the mean serum calcium levels and subjective symptoms were similar (32).

Although mild-moderate hypercalcemia is frequent in (PHP), it should be noted that it can be severe and refractory to maximum medical treatment requiring emergency surgical intervention. In addition, not being one of the most frequent reasons, severe hypercalcemia due to PHP should be considered as an important cause of metabolic encephalopathy.

Concept: Umut Mousa, **Design:** Hasan Sav, **Data Collection or Processing:** Varol Esatoğlu, Turgut Küçük, Sonuç Büyük, **Analysis or Interpretation:** Sonuç Büyük, **Literature Search:** Osman Köseoğluları, **Writing:** Pembe Okaygün, Umut Mousa, **Peer-review:** External and Internal peer-reviewed, **Conflict of Interest:** No conflict of interest was declared by the authors, **Financial Disclosure:** The authors declared that this study has received no financial support.

References

1. James L Lewi, III, MD, Fluid and Electrolyte Metabolism, Primary Hyperparathyroidism, The Merck Manual Nineteenth Edition.
2. Bilezikian JP, Brandi ML, Rubin M, Silverberg SJ. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. J Intern Med 2005;257:6-17.
3. Bandeira FB, Griz L, Caldas G, Bandeira C, Freese E. From mild to severe primary hyperparathyroidism: the Brazilian experience. Arq Bras Endocrinol Metab 2006;4:657-663.
4. Rodgers SE, Lew JI, Solorzano CC. Primary hyperparathyroidism. Curr Opin Oncol 2008;20:52-58.
5. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg 2005;132:359-372.
6. Marcocci C, Cetani F. Primary Hyperparathyroidism, N Engl J Med 2011;365:2389-2397. December 22, 2011 DOI: 10.1056/NEJMcp1106636
7. Bonesci M, Erba M, Beretta L, Miani S, Bortolani EM. Primary Hyperparathyroidism and acute pancreatitis. A rare clinical association. Miner Chir 1999;54:451-454
8. Smith MD, Pawlak M, Pantanowitz DP, Botha RJ. Hyperparathyroidism and chronic pancreatitis. S Afr J Surg 1999;37:12-14.
9. Carnaille B, Oudar C, Pattou T, Combemale F, Rocha J, Proye C. Pancreatitis and primary hyperparathyroidism: forty cases. Aust N Z J Surg 1998;68:117-119.
10. Brandwein SL, Sigman KM. Case report: milk-alkali syndrome and pancreatitis. Am J Med Sci 1994;308:173-176.
11. Ginn DR, Cate J, Tootle K, Salazar S, Watson S. Parathyroid adenoma manifested as pancreatitis and poliuria. South Med J 1991;84:1023-1029.
12. Kelly TR. Relationship of hyperparathyroidism to pancreatitis. Arch surg 1968;108:267-264.
13. Cho JW, Seligson U, Somell A. Pancreatic function in patient with hyperparathyroidism. Acta Chir Scand 1985;151:323-325.
14. Paul Chodack MD, Joseph N. Attie MD, Martin G Groder MD. Hypercalcemic Crisis Coincidental with Hemorrhage in Parathyroid Adenoma.Arch Intern Med. 1965;116:416-423. doi:10.1001/archinte.1965.03870030096016
15. Ziegler R. Medizinische Universitätsklinik und Poliklinik, Heidelberg, Germany. Hypercalcemic crisis. J Am Soc Nephrol 2001;12:S3–S9.
16. Cannon J, Lew JI, Solorzano CC. Parathyroidectomy for hypercalcemic crisis: 40 years' experience and long term outcomes. Central Surgical Association. Surgery 2010;148:807-813.
17. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, Pessin MS, Lamy C, Mas JL, Caplan LR. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494-500.
18. Khosla S. Hypercalcemia and Hypocalcemia. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, Editors. Harrison's Principles of Internal Medicine, 18th ed. McGraw-Hill Education, 2012
19. Kaplan PW. Reversible hypercalcemic cerebral vasoconstriction with seizures andblindness: a paradigm for eclampsia? Clin Electroencephalogr 1998;29:120-123.
20. Ahmed SH, Wai P, Silverdale M. Posterior encephalopathy: an uncommonmanifestation of calcium toxicity. Indian J Endocrinol Metab 2012;16:318-320.
21. Kim JH, Kim MJ, Kang JK, Lee SA. Vasogenic edema in a case of hypercalcemiainducedposterior reversible encephalopathy. Eur Neurol 2005;53:160-162.
22. Au S, Dunham M, Godinez T. Treatment of medically refractory hypercalcemic crisis. Int J Artif Organs 2012;35:538-541.
23. Giani L, Lovati C, Bana C, Cova I, Angeli FD, Mariotti C, D'Alessandro, Mariani C. Neurological department, Luigi Sacco Hospital, University of Milan, Milan, Italy. Sub-acute posterior reversible encephalopathy associated with extrapyramidal signs induced by primary hyperparathyroidism: A case report and a revision of literature. International Neuropsychiatric Disease Journal 2014;2:13-20.
24. Bartynski WS. Posterior Reversible Encephalopathy Syndrome, Part 1: Fundamental Imaging and Clinical Features. Am J Neuroradiol 2008;29:1036-1042.
25. Rashid G, Bernheim J, Green J, Benchetrit S. Parathyroid hormone stimulates theendothelial nitric oxide synthase through protein kinase A and C pathways. NephrolDial Transplant 2007;22:2831-2837.
26. Rashid G, Bernheim J, Green J, Benchetrit S. Parathyroid hormone stimulates theendothelial expression of vascular endothelial growth factor. Eur J Clin Invest 2008;38:798-803.
27. Chen HI, Yeh DY, Kao SJ. The detrimental role of inducible nitric oxide synthase in thepulmonary edema caused by hypercalcemia in conscious rats and isolated lungs. JBiomed Sci 2008;15:227-238.
28. Bartynski WS, Grabb BC, Zeigler Z, Lin L, Andrews DF. Watershed imaging features andclinical vascular injury in cyclosporin A neurotoxicity. J Comput Assist Tomogr 1997;21:872–880.
29. Schwartz RB, Bravo SM, Klufas RA, Hsu L, Barnes PD, Robson CD, Antin JH. Cyclosporine neurotoxicity and itsrelationship to hypertensive encephalopathy: CT and MR findings in 16cases. AJR Am J Roentgenol 1995;165:627–631.
30. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. AJNR Am J Neuroradiol 2008;29:1036-1042.
31. Hedna VS, Stead LG, Bidari S, Patel A, Gottipati A, Favilla CG, Salardini A, Khaku A, Mora D, Pandey A, Patel H, Waters MF. Posterior Reversible Encephalopathy Syndrome(PRES) and CT perfusion changes. Int J Emerg Med 2012;5:12.
32. Amin AL, Wang TS, Wade TJ, Yen TW. Normal PTH levels in primary hyperparathyroidism: still the same disease? Ann SurgOncol 2011;18:3437-3442.