Brain calcification due to secondary hyperparathyroidism in a child with chronic renal failure

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Secondary hyperparathyroidism (SHPT) has been better treated over the last decades, but the rate of metastatic calcifications, which were rarely seen before, was significantly increased in dialysis patients. The presence of uncontrolled SHPT, disorders of calcium (Ca) and phosphorus homeostasis and the common usage of large doses of vitamin D and Ca- containing phosphate binders may all contribute to the metastatic calcifications of soft tissues and vasculature leading to some life-threatening complications. Although the metastatic lung, heart, kidney, intestinal wall, skin, eye and soft tissue calcifications have been commonly reported in adults and also in children undergoing dialysis, the central nervous system calcification is a very rare condition. We report here a pediatric hemodialysis patient who presented with severe neurological findings due to the metastatic brain calcification secondary to his uncontrolled hyperparathyroidism.

Key words: secondary hyperparathyroidism, metastatic calcification, dialysis, children.

Although secondary hyperparathyroidism (SHPT) has been better treated over the last decades, the rate of metastatic calcifications, which were rarely seen before, was significantly increased in dialysis patients[1,2]. This changing pattern of uremic bone disease may be explained by the large amount of calcium (Ca) transfer resulting from the high dose calcitriol treatment, Ca excess during dialysis and the common usage of Ca-containing phosphate binders[1,3]. The metastatic calcification of different organs such as lung, heart, kidney, intestinal wall, skin, eye and soft tissue has been reported in both the adult and pediatric patient population undergoing dialysis, but neurological disease related to the metastatic calcification of central nervous system (CNS) is a very rare condition[2-6].

Here we report a pediatric hemodialysis patient who presented with severe neurological findings due to the metastatic brain calcification secondary to his uncontrolled HPT.

Case Report

A 16-year-old boy presented in June 2001 with facial weakness, restricted lateral gaze, difficulty in speaking, and slowness of motion. He had been undergoing hemodialysis three times a week for four years with the diagnosis of end-stage renal failure (ESRF) secondary to nephronophthisis that had been diagnosed by renal biopsy 10 years previously. From the beginning of hemodialysis in 1997, intravenous (IV) calcitriol (3 μg in a week) and 4 g calcium carbonate per day associated with the phosphorus-restricted diet were started to inhibit the high intact parathormone (iPTH) levels and to regulate the Ca and phosphorus (P) metabolism. During his SHPT therapy, he was regularly monitored at two-month intervals for serum Ca, P and iPTH levels. Calcitriol dosage was increased (maximum 9 μg in a week) when the patient's iPTH level was three-fold higher than normal, and Ca-containing phosphate binder and calcitriol were interrupted when his Ca x P product was higher than 70.

We did not observe any hypercalcemic episode in which serum Ca level was higher than 10.5 mg/dl, and serum iPTH levels were consistently high and changed from 243.5 to 2090 pg/ml at different follow-up visits during four years. Serum Ca remained between 8.5 to 10.5 mg/dl, and serum P level was

5.5 to 7.2 mg/dl. The serum Ca, P, Ca x P products and the iPTH levels of the patient are summarized in Table I. Diffuse hyperplasia of the parathyroid gland was observed in parathyroidectomy operation he admitted to our outpatient clinic with vomiting, headache and right facial paralysis. Immediately after the first neurological event, left facial paralysis

Table I. Ca, P, iPTH Values, and Calcitriol and Ca-Carbonate Doses of the Patient

Date	Ca (mg/dl)	P (mg/dl)	iPTH (pg/ml)	Calcitirol (μg/kg dose, 3 times weekly)	Ca-carbonate (g/day)
18.02.1997	8.7	6	900	1	4
18.03.1997	8.8	6.8	500	1	4
20.02.1998	9.7	5.3	243.5	0.5	3
11.08.1998	9.7	4.6	650.8	1	3
14.09.1999	10.5	7.2	1120.8	–	–*
01.02.2000	8.5	6.6	1522	2	3
08.05.2000	8.5	4.7	2090	3	3
14.06.2000	9	6.3	1788	3	3
31.08.2000	8.9	5.6	1459	3	3
19.09.2000	9.1	6	1812	3	3
11.10.2000	9.6	8.5	1875	–	–*
04.12.2000	8.9	6.2	1021	3	3
09.05.2001	8.7	5.8	1123	3	3
06.7.2001	9.9	7	378	–	–*

*Sevelamer was started.
Ca: calcium, P: phosphorus, iPTH: intact parathormone.

parathyroid gland scans, but there was no active lesion suggestive of parathyroid adenoma in all four evaluations which were performed within the previous three years. Although no parathyroid adenoma was detected, early subtotal parathyroidectomy operation was planned due to the uncontrolled iPTH levels suggestive of tertiary hyperparathyroidism in the patient. The operation could not be performed due to parental disapproval. Bone mineral density was measured in January 2001, and it revealed severe osteoporosis. Calcitonin was started in addition to IV calcitriol and Ca-based treatment. Due to the severe osteoporosis, spontaneous right femoral neck fracture occurred in the patient, and he was operated in May 2001 while being treated with 6 μg/week IV calcitriol, Ca carbonate 4 g per day, and calcitonin 100 μg per day; iPTH was 1123 pg/ml, Ca x P was 50. We performed a new parathyroid scan which revealed a pathological activity uptake at the left lower pole. A subtotal parathyroidectomy was planned for the patient. His SHPT treatment consisted of low Ca dialysis, IV calcitriol 9 μg/week, and calcitonin 100 μg/day. Furthermore, Ca-containing phosphate binders were discontinued and hyperphosphatemia was managed by sevelamer. While he was preparing for the occurred in the patient. In his neurological examination, he had facial diplegia and bilateral ophthalmoplegia with the eye movements restricted to the outside. Inflammatory markers, viral studies, and cerebrospinal fluid findings were all normal. His cranial magnetic resonance imaging (MRI) demonstrated some suspicious ischemic findings, but did not verify any lesion leading to all these symptoms. Serious axon losses in both facial nerves were determined by electromyography. The calcifications at conjunctiva and limbus were detected in ophthalmological examination. In spite of the normal cranial MR findings, cranial computerized tomography (CT) revealed diffuse calcifications at the falx and both tentorial layers (Fig.1).

Due to the suspicious calcifications demonstrated by echocardiography, he underwent cardiac MRI and calcifications on the mitral valve were detected (Fig. 2).

Physiotherapy was recommended, and diphenyl-hydantoin was started for the prophylaxis of convulsive attacks. At the last evaluation of the patient, there was no regression of neurological symptoms, iPTH level was 1770 pg/ml, and Ca x P was 65; calcitriol dose was increased to 12 μg/week which was reported

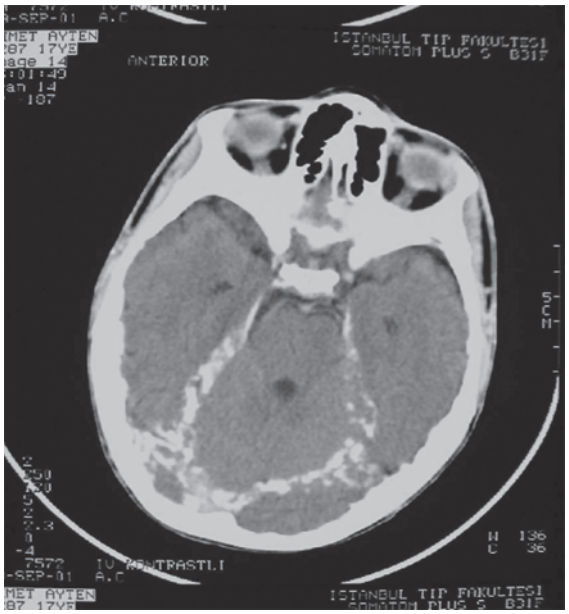

Fig. 1. Diffuse calcifications at falx and both tentorial layers on cranial magnetic resonance imaging.

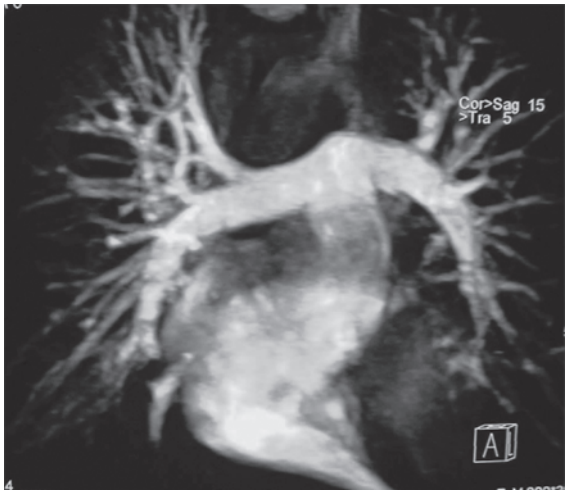

Fig. 2. Calcifications on the mitral valve on cardiac magnetic resonance imaging.

as the highest calcitriol treatment dose in this field. The parents did not accept the subtotal parathyroidectomy operation and the patient was lost to follow-up.

Discussion

Children with growing bones are most susceptible to the effects of uremia on bone metabolism, and the control of uremic bone disease has always been the most difficult approach in the management of a child with ESRF. Over the last 20 years, we have been able to better treat SHPT due to a deeper understanding of the pathogenesis of uremic bone disease.

It is worth emphasizing that even in the early years when SHPT was more common, soft tissue and vascular metastatic calcifications were not so frequent compared to the present. Despite all advances in treatment, the reported incidence of metastatic calcifications in uremic patients has significantly increased, and this paradoxical problem may not be a coincidence[1].

The presence of SHPT, disorders of Ca and P homeostasis and the common usage of large doses of vitamin D (vit D) and Ca-containing phosphate binders may all contribute to the metastatic calcifications of soft tissues and vasculature leading to life-threatening complications in dialysis patients. Grekas et al.[7] evaluated the effective treatment of SHPT with IV administration of calcitriol in hemodialysis patients. The patients with iPTH higher than 865 pg/ml were given 12 μg/week IV calcitriol. Their study demonstrated that the titration of IV calcitriol dosage according to the severity of SHPT is an effective and safe treatment of SHPT in chronic hemodialysis patients.

In the study of Costa et al.[8], the effects of calcitriol on parathyroid function and bone re-modelling were evaluated in hemodialysis patients with SHPT, and the dose of calcitriol was titrated up to a maximum of 12 μg/week. The authors showed that calcitriol had non-uniform effects on parathyroid function and bone re-modelling in uremic patients. In this study, disturbances of bone re-modelling with profound alterations in ionic balance, which could have negative implications with respect to extra-skeletal calcification, were frequently observed in calcitriol non-responder patients. In several other reports regarding the treatment of SHPT and the pathogenetic mechanisms of metastatic calcification in uremic patients, it has been suggested that metastatic tissue and vascular calcification is an active process rather than a passive mineral precipitation, and it is believed that the cells expressing an osteoblastic phenotype may be of central importance in this issue [2].

To avoid the usage of Ca-containing phosphate binder, sevelamer, a Ca-free phosphate binder, might be preferred in most of the patients with

some risks for hypercalcemia and calcifications[9]. Furthermore, recent studies about lanthanum carbonate and iron-based compounds, which are also Ca-free phosphate binders, have significant promise in this field[9].

The primary disease leading to ESRD, such as tubulointerstitial disorders, has been known as a significant factor in the development of severe hyperparathyroid bone disease[10-12].

Nephronophthisis, which has been known as a familial tubulo-interstitial nephropathy, might have had an association with uncontrolled SHPT in our patient. However, the findings of our patient may be mainly discussed from two aspects. Firstly, the presentation of our patient with an unusual site of tissue calcification shows that SHPT may be associated with signs of severe CNS disorder. We believe that although CNS calcification related to SHPT in pediatric dialysis patients is a very rare condition, uremic children with unexplained neurological signs or symptoms should be checked for HPT, and possible metastatic calcifications should be verified by CT imaging. Secondly, although severe hypercalcemia and hyperphosphatemia were not present and serum Ca x P product was not higher than 70 during follow-up, metastatic brain, eye and heart calcification occurred four years after the initiation of high dose IV vitamin D replacement. These findings suggest that the soft tissue calcifications observed in our patient could have developed in association with vitamin D therapy unrelated with the high serum Ca levels.

In the study of Block et al.[1,] it has been shown that the current treatment protocol for SHPT is ineffective for a relatively large group of dialysis patients. There were several patients with soft tissue calcification despite the serum Ca x P product below 70 in their study population, and they suggested that prevention of uremic calcifications should assume primary importance when evaluating the risks associated with elevated levels of P, Ca x P and iPTH. They recommended that target levels should be between 9.2-9.6 for Ca, 2.5-5.5 mg/dl for P, less than 55 for Ca x P product, and 100-200 pg/ml for iPTH[1].

Are we mis-managing Ca and P metabolism in renal failure? There is no exact answer to this question, and it may not be answered exactly until the pathogenesis of the soft tissue and vascular calcification of the dialysis patients is better understood. However, in light of the reported patient's findings, we suggest that calcitriol and Ca-carbonate may be safely used for the management of SHPT only if a negative Ca balance is maintained during renal replacement therapy. We also believe that the early decision of parathyroidectomy operation in uncontrolled SHPT may prevent severe complications of renal osteodystrophy.

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