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The 463th International Symposium on Therapy was held at the Kioi Forum in Tokyo on March 21, 2024. Dr. Kouichi Ito, Managing Director of the International Medical Society of Japan (IMSJ), presided over the meeting.

Up-to-date management of parathyroid disease

■Introductory Message from the Chair

K. Ito, MD, PhD. Managing Director, IMSJ

■Lecture Ⅰ

Surgical Treatment for Renal Hyperparathyroidism

Yatsuka Hibi MD, PhD
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■Lecture Ⅱ

Management and surgical treatment of primary hyperparathyroidism

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Introductory Message from the Chair

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Lecture I

Surgical Treatment for Renal Hyperparathyroidism

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It has been recognized that the mineral metabolic disorder Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), which occurs in chronic kidney disease, has a significant impact on life expectancy not only through bone abnormalities but also through calcification of blood vessels or cardiac valve leaflets. Secondary hyperparathyroidism (SHPT) caused by chronic kidney disease has also been incorporated into the concept of CKD-MBD and treatment strategies need to be considered. In other words, it is now important to control serum P and Ca levels to the recommended control targets with the endpoint of improving life expectancy, rather than simply lowering blood PTH levels to improve bone lesions. The CKD-MBD guidelines of the Japanese Society for Dialysis Therapy recommend maintaining serum P, serum corrected Ca, and serum intact PTH levels within the recommended control targets, in that order of priority.

When blood intact PTH exceeds 500 pg/mL, the parathyroid glands are likely to be transformed into nodular hyperplastic glands, which are more likely to become resistant to vitamin D therapy. Therefore, the CKD-MBD guidelines recommend parathyroidectomy (PTx) for severe SPHT (intact PTH >500 pg/mL or whole PTH >300 pg/mL) that is resistant to medical therapy. Since SPHT can cause subjective symptoms such as osteoarthralgia, muscle weakness, and pruritus, the indication for PTx should be considered with the aim of improving these symptoms as well. The guidelines also state that even if a patient's blood PTH level does not reach the above, it is reasonable to consider PTx when hyperphosphatemia or hypercalcemia exceeding the target values for management is difficult to correct. The PTx procedures for SPHT include subtotal parathyroidectomy, total parathyroidectomy (without autograft), and total

parathyroidectomy followed by autograft. Overseas reports have shown that there is no clear superiority between subtotal parathyroidectomy and total parathyroidectomy followed by autograft. However, in patients with SPHT in Japan, where opportunities for renal transplantation are rare and patients are often required to undergo long-term dialysis even after PTx, total parathyroidectomy followed by autograft is often chosen, accounting for approximately 80% of all cases.

On the other hand, the Ca-receptor agonist, cinacalcet, was approved in Japan in 2008 for the treatment of SHPT in patients on maintenance hemodialysis. Therefore, it can be expected to suppress calcification of the cardiovascular system as well as PTx. Since the number of cases in which SHPT can be controlled by administration of cinacalcet has been increasing in cases where PTx was previously indicated, PTx is now limited to cases in which the patient is unable to continue treatment due to gastrointestinal symptoms or other side effects, or when the patient is refractory to treatment with cinacalcet. According to the PTx Study Group for Secondary Hyperparathyroidism, the annual number of PTx cases in Japan has decreased from a peak of 1771 cases in 2007 to 123 cases in 2018. Cinacalcet is an oral formulation, so there are some cases patients may not actually be taking it, but the introduction of intravenous Ca-receptor agonists such as etelcalcetide in 2017 has allowed for more stable dosing in dialysis patients. Moreover, with the approval in 2018 of evocalcet for secondary hyperparathyroidism under maintenance dialysis with less frequent gastrointestinal symptoms and other indications, the number of cases requiring PTx is expected to be even more limited in the future. However, it has been reported that PTx in post-cinacalcet use cases poses a risk of difficulty in identifying and of damaging the recurrent laryngeal nerve due to adhesions to surrounding tissues caused by changes such as hemorrhagic infarction and fibrosis of the parathyroid gland, and that PTx is a cost-effective option from a medical economic perspective.

After kidney transplantation, the curative treatment for end-stage chronic kidney disease, SHPT is expected to improve, and after about one year, fluctuations in serum Ca and P levels are expected to decrease. However, Egbuna et al. reported that 24% of patients with intact PTH remained above 130 pg/mL one year after kidney transplantation, and patients with a corrected Ca level above 10.5 mg/dL had a significantly higher risk of graft loss. Based on this, the CKD-MBD guidelines recommend that the indication for persistent hyperparathyroidism after kidney transplantation (tertiary hyperparathyroidism;THPT), is persistently hypercalcemia (corrected Ca ≥ 10.5 mg/dL) and high PTH levels (above the upper reference limit) even one year after kidney transplantation, in which case PTx should be considered. Regarding when PTx for THPT should be performed after kidney transplantation, some argue that early PTx after kidney

transplantation should be avoided because of the concern that PTx may cause a sudden decrease in eGFR, which was apparently elevated due to hypercalcemia, while others argue that this eGFR decrease is transient and does not affect the long-term graft survival, and that it is better to remove the harmful effects of hypercalcemia and other factors on the transplanted kidney at an early stage. As for the technique, it is reasonable to perform total parathyroidectomy followed by autograft, considering the risk of recurrence and reoperation, since there are few opportunities for re-transplantation after graft function is abolished and cinacalcet is not approved for THPT in Japan. Even if SPHPT is well controlled by Ca-receptor agonists prior to kidney transplantation, there is concern that it may be discontinued after kidney transplantation, because it is not approved for THPT in Japan, resulting in worsening of THPT. Therefore, we believe that PTx should be performed in advance when a large gland that appears to be a nodular hyperplastic gland is found prior to kidney transplantation.

Lecture II

Management and surgical treatment of primary hyperparathyroidism

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1. Background

In Japan, primary hyperparathyroidism is reported to affect approximately 1 in 2,000 to 3,000 people, and it is more common in middle-aged and older women. In the 1970s, it was a rare disease, but it is now often detected asymptomatically during health checkups and other tests.

2. Subjective symptoms

The main symptoms are those caused by hypercalcemia, urinary stones, and bone lesions.

① Symptoms due to hypercalcemia

As a result of impaired urine concentration, polyuria, dry mouth, and polydipsia appear. Gastrin secretion is also increased, resulting in gastrointestinal symptoms

such as nausea, anorexia, reflux esophagitis, and peptic ulcers.

② Symptoms due to urolithiasis

Increased calcium excretion in the urine and inhibition of bicarbonate ion reabsorption make the urine alkaline, which causes nephrolithiasis due to calcium oxalate. Lower back pain, colic, and hematuria appear. Decreased renal function is also often observed.

③ Symptoms due to bone lesions

A lesion called osteitis fibrosa cystica is observed due to increased bone turnover and the appearance of excessive osteoclasts. Bone mass, especially cortical bone mass, decreases, leading to osteoporosis.

3. Points to note during diagnosis

The criteria for diagnosis are hypercalcemia, high parathyroid hormone levels, and urinary calcium excretion (FECa) of 1% or more. If urinary calcium excretion (FECa) is less than 1%, familial or acquired hypocalciuric hypercalcemia is suspected, and no treatment is necessary. On the other hand, care must be taken, because FECa will be low in cases of worsening renal function or vitamin D deficiency.

4. Points to consider when deciding on surgical treatment

After primary hyperparathyroidism is diagnosed, it is necessary to evaluate whether surgery is appropriate, where it is localized, and whether it is hereditary.

① Regarding surgical indications

Recently, asymptomatic mild hypercalcemia has often been detected, and the indications for surgery in such cases are being debated from the viewpoint of prognosis and surgical complications. According to the NIH guidelines, the indications include: serum calcium level +1 mg/dL or higher than the upper reference limit; bone density T score is -2.5 or higher; vertebral fracture is detected on imaging; the estimated glomerular filtration rate (eGFR) is <60 cc/min; and urinary calcium excretion is 250 mg/day or higher in women. For men, surgery is recommended if any one of the following indications is met: urinary calcium excretion of 350 mg/day or more, kidney stones or calcareous deposits are seen on imaging, or age under 50 years.

② Localization

The basic tests are neck ultrasound and 99mTc-methoxyisobutylisonitrile (MIBI) scintigraphy. Neck ultrasonography shows that the dorsal side of the thyroid gland

is flat, oval, with a clear border, and internally hypoechoic. The accumulation in the parathyroid glands on the MIBI test depends on the content of mitochondria-rich eosinophilic cells, and a large amount is taken up in adenomas with many eosinophilic cells. Recently, localization has become more accurate by simultaneously merging single-photon emission CT (SPECT) images. In addition, CT examination (thin-slice imaging) and MRI are useful for locations anatomically difficult to detect by cervical ultrasound examination (such as the tracheoesophageal groove, mediastinum, and just below the thyroid cartilage).

③ Hereditary

Hereditary hyperparathyroidism is observed in approximately 5-10% of cases of primary hyperparathyroidism. In addition to multiple endocrine neoplasia type 1 (MEN1), hyperparathyroidism jaw tumor syndrome is also recognized. If it is hereditary, the surgical procedure requires a complete gland search on both sides, and screening for related diseases is also required.

5. Changes in surgical techniques

The surgical technique has changed over the years. In the 1970s, bilateral (all gland) searches were performed, but the surgery was long and carried the risk of bilateral recurrent laryngeal nerve paralysis. Currently, minimally invasive parathyroidectomy (focused exploration) has become mainstream. Since the mid-1990s, it has become possible to accurately diagnose the site using MIBI scintigraphy and by measuring intraoperative parathyroid hormone levels. As a result, the incision line is small, and the surgery can be completed in a short time, making it less invasive.

6. Future challenges

The success rate is low when the pathological gland is not obvious, and patients may hesitate to undergo surgical treatment, especially if they are elderly and have many underlying diseases. Medical treatment is performed, but it is necessary to compare its outcomes with those of surgical treatment.