Chapter 10
Indications for Parathyroidectomy

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The parathyroid glands were first discovered in 1850 by Sir Richard Owen, the curator of the Natural History Museum of London. He described a "small compact yellow glandular body attached to the thyroid at the point where the veins emerge" following the autopsy of a rhinoceros [1]. German pathologist Rudolph Virchow may have identified the parathyroid gland in 1863 when describing the cervical region, but it was not until 1880 that Ivar Sandström, a medical student at the time, definitively demonstrated the existence of parathyroid glands in a human through meticulous cadaveric dissection and documentation [1, 2].

Felix Mandl, a Viennese surgeon, was the first to demonstrate the relationship of the parathyroid glands and their removal with calcium homeostasis and bone health. He also demonstrated successful control of hypercalcemia with resection of a parathyroid adenoma in 1925. Mandl, along with David Barr and Harold Bulger, helped develop and define the clinical presentation of hyperparathyroidism in the late 1920s.

Parathyroid-Related Hypercalcemia

Typically, there are four parathyroid glands, two superior and two inferior, each weighing 30–50 milligrams [3–5]. Accessory or supernumerary parathyroid glands are found in approximately 13% of individuals at autopsy [3, 4]. Ectopic parathyroid tissue occurs in 15%–20% of humans [5]. Ectopic parathyroid glands can be

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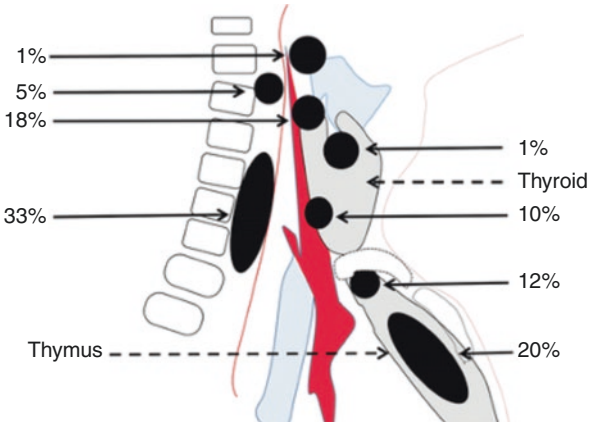

Fig. 10.1 Sagittal view of the neck depicting locations of ectopic parathyroid tissue. The carotid artery, thyroid cartilage, cervical vertebrae, and sternum are depicted as well. Frequency of ectopic location is depicted with percentages that ectopic tissue is found in noted location

located anywhere along the tract of thymic descent [1–5]. Figure 10.1 depicts common ectopic parathyroid tissue locations and their relative frequencies [6].

The parathyroid glands develop during the fifth and sixth weeks of gestation. The inferior parathyroid glands arise from the third pharyngeal pouch, and the superior parathyroid glands arise from the fourth pharyngeal pouch [6–10]. The inferior parathyroid glands migrate with the thymus caudally and medially. This accounts for the more variable location of these glands.

Parathyroid hormone helps regulate the body's calcium homeostasis by affecting bone mineral turnover, renal calcium reabsorption, and dietary enteral calcium absorption. As calcium measurements have become part of routine blood work, there is an emerging trend of earlier disease presentation and an increased incidence of normocalcemic primary hyperparathyroidism. Some studies demonstrate clinical benefit to surgical management in this population, given its cost-effectiveness, versus continued chemical monitoring and the value of prevention of end-organ damage [9, 10]. Stephen et al. found that surgical management in asymptomatic individuals with normocalcemia hyperparathyroidism was associated with decreased rates of renal dysfunction, osteoporosis, and cardiovascular disease later in life [4].

The most common cause of primary hyperparathyroidism, accounting for 85% of cases, is a single parathyroid adenoma [5, 11]. In some cases, there is a second adenoma that is also hypercellular and producing excessive parathyroid hormone but has been suppressed by the first adenoma. Multiple synchronous parathyroid adenomas have been reported in up to 10% of individuals [1, 11]. Four-gland hyperplasia accounts for approximately 15% of primary hyperparathyroidism cases, followed by parathyroid carcinoma in <1% of primary hyperparathyroidism cases [7].

Parathyroid carcinoma may present as a hypercalcemic crisis. The cause of parathyroid carcinoma is unknown, but it is associated with several syndromes and known genetic mutations. HRPT2/CDC73 is a tumor suppressor gene located on chromosome 1 and encodes parafibromin, a protein that is involved in regulation of gene expression and inhibition of cell proliferation [12, 13]. Mutations in this gene have been linked to both familial and sporadic cases of parathyroid carcinoma.

Mutations in PI3K, AKT, and MTOR pathways have also been demonstrated with whole-exome sequencing. Parathyroid carcinoma is associated with higher serum levels of parathyroid hormone, often five to ten times higher than levels associated with single or multiple adenomas. It is also associated with significantly higher serum calcium levels (greater than 14 mg/dL) [12, 13].

Effects of PTH-Mediated Hypercalcemia

Parathyroid hormone is crucial to vitamin D homeostasis. Normal vitamin D absorption and activation start with dietary intake of D_2 or D_3 or 7-dehydrocholesterol activation with 290–315 nm ultraviolet B radiation (sunlight exposure to the skin) [14]. The liver then hydroxylates it to form 25-hydroxyD. Parathyroid hormone, released in response to low serum calcium levels, causes renal hydroxylation of 25-hydroxyD to $1,25(OH)_2D$, the bioactive form [14]. Secretion of parathyroid hormone signals increased renal absorption of calcium, increased renal excretion of phosphate, and increased synthesis of $1,25(OH)_2D$, which increases intestinal absorption of calcium and binds to osteoblasts, activating a signaling cascade which prevents bone growth [14, 15]. With normal parathyroid glands, this physiology promotes appropriate calcium homeostasis. In primary hyperparathyroidism, this pathophysiology leads to elevated serum calcium levels. Hypercalcemia is important to address due to its ability to cause end-organ damage when levels remain elevated over time. Assadipour et al. reported that 62% of patients demonstrated evidence of at least one type of end-organ damage related to hypercalcemia within 5 years of a primary hyperparathyroidism diagnosis [11].

Hypercalcemia can negatively impact renal function through direct injury resulting from nephrocalcinosis and hypercalciuria. It can also lead to chronic renal insufficiency indirectly secondary to nephrolithiasis. Renal function is often calculated and reported as the estimated glomerular filtration rate (eGFR), and primary hyperparathyroidism is associated with decreased eGFR even in the absence of nephrolithiasis or nephrocalcinosis. However, rates of renal dysfunction in patients with primary hyperparathyroidism are decreasing due to the trend toward early diagnosis of primary hyperparathyroidism.

Bone health is also impacted by primary hyperparathyroidism. As noted above, parathyroid hormone binds to osteoblasts and stimulates a signaling cascade that results in bone resorption. In the absence of new bone formation, bone loss becomes permanent, and osteopenia followed by eventual osteoporosis ensues [15, 16].

Hypercalcemia as a result of primary hyperparathyroidism can also have a detrimental effect on the cardiovascular system. Several studies have demonstrated increased rates of atherosclerosis, hypertension, left ventricular hypertrophy, heart failure, arrhythmia, and valvular calcific disease [17, 18]. The mechanism behind at least some of this dysfunction is thought to be due to excess parathyroid hormone action on G-protein-coupled receptors in the heart resulting in changes to myocyte contractility, hypertrophy, and proliferation (this also likely leads to endothelial

changes in the vasculature) [18]. Valvular disease can also develop from the direct effect of calcium deposition [17].

When to Intervene

Hypercalcemia can be managed medically, but the definitive treatment for primary hyperparathyroidism is surgery. Medical management is limited to patients who are not surgical candidates or choose not to have surgery. Cinacalcet is the only medication that has been demonstrated to decrease serum calcium levels without changing serum parathyroid hormone levels demonstrably and with no effect on bone mineral density. [9] Bisphosphonate therapy has been demonstrated to improve bone mineral density, and alendronate, specifically, has been shown to improve density in the lumbar spine for patients with nonsurgically managed primary hyperparathyroidism without affecting serum calcium levels [9]. In the setting of critically high hypercalcemia, aggressive intravenous hydration with diuresis or even dialysis can palliate the situation until appropriate medication can be given or surgery can be performed.

Indications for Surgery

Historically, patients were identified with primary hyperparathyroidism only at the point that they demonstrated clear sequelae of the disease, such as pathologic fractures or recurrent nephrolithiasis. However, with patients now typically being identified earlier in their disease course, the value and need for surgery have become a more relevant clinical question. There is widespread agreement that "symptomatic" patients, often defined as experiencing a pathologic fracture or nephrolithiasis, should undergo surgery. The benefit of surgery in these patients is felt to be manifest.

Greater debate exists over the value of surgery in so-called "asymptomatic" patients. The National Institutes of Health (NIH) has published a series of consensus guidelines addressing this cohort. In the most recent version, published in 2014, surgery was recommended for asymptomatic patients who were younger than 50 years old, had a serum calcium of 1 mg/dL or more above the upper limit of normal, demonstrated a bone mineral density T-score on DEXA less than or equal to −2.5, had a creatinine clearance less than 60 milliliters per minute or a 24-hour urine calcium greater than 400 mg/d, or had nephrolithiasis or nephrocalcinosis identified on radiology imaging [19]. Recently, the American Association of Endocrine Surgeons (AAES) published their consensus guidelines on parathyroidectomy [20]. Those recommendations largely mirror the NIH suggestions.

However, the question of who should be considered "asymptomatic" remains an open debate. Data continues to accumulate which demonstrate that "asymptomatic" patients are often not truly asymptomatic and that many patients benefit from surgery regardless of symptoms. Many additional symptoms, such as neurocognitive

impairment and sleep disturbances, are in at least some patients attributable to their primary hyperparathyroidism. Consequently, the AAES guidelines extend their recommendations beyond those of the NIH. For patients that exhibit neurocognitive or neuropsychiatric symptoms attributable to hyperparathyroidism, surgery is recommended. Additionally, other possible manifestations of the disease, including muscle weakness, abnormal sleep patterns, and gastroesophageal reflux, can be considered when weighing the value of possible surgery. Debate about the optimal indications for surgery will continue until more definitive evidence regarding the benefits of surgery is gathered.

In the setting of reoperative surgery, in which the risk of failure and complications is greater, the threshold to proceed with surgery should be greater than in primary surgery. The American Head and Neck Society and British Association of Endocrine and Thyroid Surgeons (AHNS/BAETS) recently published guidelines on reoperative management of parathyroid disease [21] and recommend that surgeons carefully reassess the indications and potential benefits of surgery in the context of the greater complexity of reoperative cases.

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