Primary hyperparathyroidism (PHPT) is a common endocrine disorder that has demonstrated a recent increase in incidence rate — likely due to PHPT screening in patients being evaluated for osteoporosis. If untreated, approximately 30% of patients with PHPT will demonstrate disease progression. Some patients can have associated significant morbidity due to osteoporotic fractures, nephrolithiasis, neuropsychiatric disorders and other common but nonspecific symptoms.

Although surgical excision is curative, precise preoperative localization is often challenging due to the small size and variable location of parathyroid adenomas, which can be located throughout the neck or mediastinum and are often only slightly larger than a normal gland. In up to 25% of patients, especially those with mild forms of PHPT, multigland parathyroid disease is encountered. These factors contribute to approximately 10% of patients failing initial surgery using conventional preoperative imaging techniques. In such cases, repeat surgical exploration is less likely to be successful and may impart a higher risk of complications in addition to increased expense.

In an effort to improve treatment of parathyroid disease, a multidisciplinary team of radiologists, endocrinologists and endocrine surgeons at Mayo Clinic in Rochester, Minnesota, has adopted a novel imaging technique using carbon-11-choline — $^{11}$C-choline — positron emission tomography/computerized tomography (PET/CT). $^{11}$C-choline is a nuclear medicine radiotracer approved by the Food and Drug Administration and the Centers for Medicare & Medicaid Services for restaging biochemically recurrent prostate cancer. Since its clinical introduction in 2012, $^{11}$C-choline PET/CT has demonstrated utility in a variety of disease processes and has shown particular promise in parathyroid imaging.

Ahmad Parvinian, M.D., with Diagnostic Radiology at Mayo Clinic in Rochester, Minnesota, says, "In a 2018 publication in the American Journal of Roentgenology, we summarized our experience with 7,088 $^{11}$C-choline PET/CT examinations in 2,933 consecutive patients undergoing PET/CT for biochemically recurrent prostate cancer between January 2005 and February 2016. In this group, we identified 13 patients with pathologically or laboratory-proven parathyroid adenomas."

Geoffrey B. Johnson, M.D., Ph.D., with Nuclear Medicine at Mayo Clinic in Rochester, Minnesota, elaborates: "$^{11}$C-choline PET/CT proved 100% sensitive for detection of abnormal parathyroid glands. The adenomas demonstrated maximum standardized uptake values that averaged twice as high as the adjacent thyroid glands and four times higher than the blood pool, generating visually appealing images with a high signal compared with the background.

"The lesions identified in this study averaged 9 mm by 6 mm in size and included a mediastinal ectopic adenoma as well as an adenoma weighing only 50 mg — slightly larger than the accepted upper limit of a normal parathyroid gland at 30 mg. Two patients who underwent parathyroidectomy had subsequent $^{11}$C-choline PET/CT examinations, and in both cases the focal choline uptake corresponding to the suspected adenomas resolved on the follow-up scan.

"In addition to high sensitivity for localization of abnormal parathyroid glands, the advantages of $^{11}$C-choline PET/CT over conventional parathy-
roid imaging modalities include its speed, with imaging completed in less than 15 minutes as opposed to several hours in other nuclear medicine examinations, as well as its low radiation dose relative to conventional nuclear techniques and CT. Moreover, there have been no adverse events or evidence of toxicity in the more than 3,000 patients who have undergone $^{11}$C-choline PET/CT at our institution.”

Robert A. Wermers, M.D., chair of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, adds, “Since publishing our initial experience, we have begun using $^{11}$C-choline PET/CT for preoperative localization of parathyroid adenomas in selected patients (see Figure, page 1), including those with persistent PHPT that is not localized by other imaging modalities such as ultrasonography, parathyroid scans and dynamic (4D) CT scans.

“A recent demonstration of the benefit of this new imaging method was seen in a 56-year-old woman who presented to our clinic with persistent PHPT with a serum calcium level as high as 11.7 mg/dL, hypophosphatemia, marked hypercalciuria and a parathyroid hormone that was fourfold elevated.”

Stephen D. Cassivi, M.D., M.S., with Thoracic Surgery at Mayo Clinic in Rochester, Minnesota, expands, “Multiple imaging modalities, including a neck ultrasound, parathyroid scan and 4D CT, failed to localize the source of her disease. The patient underwent $^{11}$C-choline PET/CT that revealed an ectopic mediastinal parathyroid adenoma within the thymus, accounting for her persistent hyperparathyroidism. Subsequent thoracoscopy and resection of the ectopic parathyroid gland proved curative.”

Dr. Wermers concludes, “Our experience suggests that $^{11}$C-choline PET/CT is a sensitive, safe, low-dose and fast preoperative imaging option in patients with hyperparathyroidism and suspected parathyroid adenomas. We hope to expand access to this exciting technique for more patients in the near future.”

**For more information**
In a study published in 2019 in the *World Journal of Surgery*, researchers with Endocrine Surgery at Mayo Clinic in Rochester, Minnesota, found indocyanine green fluorescence angiography to be a useful adjunct in assessing parathyroid blood supply compared with visual inspection alone (Figure).

“Indocyanine green fluorescence angiography has been a game changer in thyroid surgery,” says Melanie L. Lyden, M.D., senior author of the manuscript. “For decades, visual inspection and incising the parathyroid gland to see if it bleeds have been the only ways to validate parathyroid presence and function. Now we have real-time data that help us identify parathyroid glands and ensure that they are functioning. If they have a compromised blood supply, we can auto-transplant them to minimize the incidence of long-term dysfunction.

“Visual inspection was found to be inaccurate 15% of the time, which means that viable parathyroid glands were excised and auto-transplanted when they didn’t need to be and nonviable glands were not auto-transplanted when they should have been. We also found that when fluorescent imaging confirms well-vascularized parathyroid glands, we can be reassured that their parathyroid hormone level is adequate.”

To perform angiography after a total thyroidectomy, specialists inject patients with 3 to 4 mL of indocyanine green and the vascularity is evaluated using a Pinpoint camera — a fluorescent imaging camera that uses white light. Well-perfused parathyroid glands take up the indocyanine green and display a visible fluorescence, while glands that may have been compromised during total thyroidectomy have weak or no fluorescence, prompting auto-transplantation.

Patients with well-perfused parathyroid glands are given a score of 2, which has been predictive of normal parathyroid function immediately after thyroid surgery. Those with a compromised blood supply are given a score of 1 or 0, which may lead to auto-transplantation to preserve long-term parathyroid function.

Benzon M. Dy, M.D., a consultant with Endocrine Surgery at Mayo Clinic in Rochester, Minnesota, concludes: “It is difficult to know in the early stages of this new technology if long-term hypoparathyroidism will be prevented, given its overall low incidence. However, this objective assessment also helps to identify patients who may be at risk of short-term hypocalcemia, and allows us to initiate treatment sooner. Overall, indocyanine green fluorescence angiography is a safe and inexpensive adjunct that provides real-time data to the surgeon and may have other implications in the future as its use is expanded in patients with bulky central compartment lymphadenopathy and invasive thyroid cancers.”

**For more information**

A 49-year-old white female presented to the bone clinic at Mayo Clinic in Rochester, Minnesota, with a history of intermittent joint pains affecting her hands, feet and elbows since her 20s, periarticular growths, and bilateral conductive hearing loss. There was no history of fractures, renal dysfunction, nephrolithiasis or hypercalcemia.

Examination revealed normal midparental height, nondysmorphic body habitus, Heberden’s and Bouchard’s nodes in the fingers, and hammertoe deformities of the feet. Laboratory workup was significant for a low serum phosphorus; elevated parathyroid hormone (PTH); elevated 1,25(OH)₂-D; and reduced renal tubular reabsorption of phosphorus, or TRP (Table). Dual energy X-ray absorptiometry showed osteopenia (worst femur neck T-score: -2.3), and parathyroid sestamibi scan was nonlocalizing.

The patient was diagnosed with normocalcemic primary hyperparathyroidism (PHPT) and her symptoms were treated with vitamin D and calcium supplementation. However, a year later, she underwent removal of left and right superior parathyroid glands at another institution.

The patient returned to Mayo Clinic at age 52 with intermittent symptomatic hypocalcemia, persistent hypophosphatemia and a normal PTH. Her family history was notable for a sister who was deaf and had severe hypophosphatemic rickets, periarticular mineral deposition, and a history of normocalcemic primary hyperparathyroidism with multigland parathyroidectomy.

C-terminal fibroblast growth factor 23 (FGF23) was in the normal range, but with the concern for hereditary non-PTH mediated hypophosphatemia, intact FGF23 was tested and found to be elevated (Table).

Detailed bone radiographs demonstrated bowing of bilateral femurs (Figure 1) and periarticular calcifications in hands, elbows, knees, shoulders and feet (Figures 2a and 2b, see page 5).

The patient was evaluated by Medical Genetics staff and underwent whole-exome sequencing that identified two variants in the ENPP1 gene:
- (A) Heterozygous (HET) c.323G>T p.Cys108Phe (inherited from father)
- (B) HET c.1441C>T p.Arg481TRP (inherited from mother)

No PHEX, FGF23 or DMP1 mutations were identified, hence ruling out other forms of hereditary hypophosphatemia. The sister who had a similar but more severe phenotype had the same biallelic mutations and each of the patient’s three children had monoallelic mutations.

Vascular health screening demonstrated increased carotid intima-media thickness but no vascular calcification. The patient was treated with calcium, vitamin D-3 and calcitriol, which led to improvement in serum calcium and phosphorus.

### Discussion
Hereditary hypophosphatemia is a form of FGF23-mediated hypophosphatemia categorized as X-linked hypophosphatemia, autosomal dominant hypophosphatemic rickets or the much rarer autosomal recessive hypophosphatemic rickets (ARHR) types 1 and 2. ARHR2 is associated with deficiency of the ENPP1 enzyme, which generates pyrophosphate (PPi) from adenosine triphosphate, but its association with FGF23 is unclear. The clinical features of ARHR2 in adults include:
- Periarticular calcifications with a waxing and waning clinical course over years
- History of rickets
- Conductive hearing loss

Rickets and hypophosphatemia are mediated by FGF23 produced by bones, which decreases renal phosphate reabsorption and decreases
1-alpha hydroxylase activity. Hence a patient with hypophosphatemia, low or normal PTH, and low or inappropriately normal 1,25(OH)₂D for the level of hypophosphatemia should raise concern for FGF23-mediated hypophosphatemia.

As reported in Human Mutation in 2016, periarticular calcifications in ARHR2 are likely due to PPI deficiency, because PPI inhibits hydroxyapatite crystal deposition as well as arterial intima-media proliferation. Periarticular enthesopathy has not been previously described in patients with ARHR2 but is seen in ENPP1 knockout rodent models, as reported in Bone in 2012; we identified that the proband’s sister had enthesopathy.

PHPT has not been previously noted in patients with ENPP1 variants. Reduced 1,25(OH)₂D mediated through increased FGF23 downregulation of 1-alpha hydroxylase activity over time can lead to chronic parathyroid stimulation, which could contribute to PHPT. Our patients confirm the observation that C-terminal FGF23 can be normal but may be inappropriately so for the extent of hypophosphatemia; however, intact FGF23 is usually elevated with biallelic ENPP1 genetic variants.

Given the challenges of diagnosing hereditary hypophosphatemia based on clinical and biochemical findings, gene sequencing should be considered. Inactivating ENPP1 variants are associated with generalized arterial calcification of infancy (GACI) and less often ARHR2. Variable disease severity is reported, with infants presenting with the severe GACI while children and adults present with ARHR2, as reported in American Journal of Human Genetics in 2010 and Nature Genetics in 2003. However, such pathogenic variants are extremely rare, with only six adults with ARHR2 caused by inactivating ENPP1 variants, also reported in Nature Genetics in 2003.

Hence, our patient and her sister with inactivating compound heterozygous ENPP1 variants, one of which has been associated with GACI and reported in Nature Genetics in 2003, in addition to a novel variant not previously identified, add to the limited knowledge. This kinship suggests that compound heterozygous carriers of the HET c.1441C>T p.Arg481TRP pathogenic variant develop less severe disease than homozygous carriers, and that the protein generated by the allele altered by the HET c.323G>T p.Cys108Phe variant retains some functionality of ENPP1 enzyme.

ENPP1 may perform other functions in addition to PPI generation that may contribute to the uncommon phenotype observed. It is significant that both compound heterozygous subjects developed PHPT, a condition affecting a tissue where ENPP1 is also expressed. Homozygous biallelic mutations known to cause GACI have been associated with death in early childhood, whereas compound heterozygous mutations demonstrate survival beyond the critical early childhood period in some families.

Identification of ENPP1 mutations causing GACI or ARHR2 has increased clinical relevance due to the recent development of ENPP1 enzyme replacement therapy (INZ-701), which has demonstrated restoration of PPI to normal levels reducing complications associated with ENPP1 deficiency in rodents, as reported in Nature Communications in 2015.

**Key points**
- In hereditary hypophosphatemia, FGF23 levels should be interpreted relative to the degree of hypophosphatemia, keeping in mind the limitations of the clinically available C-terminal assay.
- Loss of function variants in genes encoding the enzyme ENPP1 cause GACI and ARHR2 as part of a phenotypic spectrum.
- Monoallelic ENPP1 variants may cause subtle biochemical and clinical findings.
• Whole-exome sequencing can be useful in the diagnosis and detection of new causative mutations of rare bone and mineral disorders.

For more information


Endocrinologist-Directed Multidisciplinary Hospital Nutrition Support Service

Mayo Clinic in Rochester, Minnesota, has 2,059 licensed beds on two hospital campuses. Each campus has a Nutrition Support Service (NSS) directed by an Endocrinology consultant with rotating house staff: an Internal Medicine resident or Endocrinology or Gastroenterology fellow trainee, dietitians, nurses, and pharmacists.

Nationally, endocrinologists are infrequently involved in hospital nutrition. M. Molly McMahon, M.D., with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, and who is also immediate past president of the American Society for Parenteral and Enteral Nutrition (ASPEN) and NSS medical director, says, “With our additional training, our expertise in metabolism makes us valuable specialists for this field. National surveys continue to report that clinicians are undertrained in nutrition. We are committed to educating rotating learners and consulting with primary service providers. We are fortunate to have institutional and divisional support, as our value results from the synergy of all disciplines. Our team has been recognized as a team of distinction by ASPEN.”

Meera Shah, M.B., Ch.B., with Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, and the endocrine rotation director for the Internal Medicine Residency, says: “Assigned cases allow house staff to learn basic nutrition principles and to apply nutrition to specific patient conditions (Table). House staff rotations are shorter in duration than other rotations, so NSS team members created case-based videos to address nutrition topics that would otherwise not be covered.”

Malnutrition, common in patients who are hospitalized, is associated with longer length of stay, poorer outcomes and higher cost of care. Nutrition support is a costly form of therapy that provides substantial benefits when used appropriately, but it also carries risks.

| Glucose management: Review for overfeeding; initiation or cessation of parenteral nutrition (PN) dextrose; dextrose from other crystalloid infusion. Account for calories provided by renal replacement therapy acid citrate-dextrose solution; medications that can affect glucose levels such as corticosteroids, propofol and sympathomimetics; and glucose trends. |
| Volume excess: Evaluate need for fluid-restricted nutrition programs. |
| Obesity, hypertriglyceridemia or both: Initiate permissive underfeeding with adequate protein. |
| Propofol use: Check triglyceride value and reassess PN fat content. |
| Re-feeding risk: Avoid overfeeding; administer thiamin; review electrolyte and mineral values and supplement as needed. |
| Diarrhea: Review drug-nutrient issues; ensure medications are administered by correct route in light of osmolality and mechanism of drug action. |
| Dialysis: Review nutrition program protein and minerals to be certain appropriate for type of dialysis. |
| Long-term PN in hospital: Choose desired central catheter for nutrition; reassess PN trace element doses; for patients with PN-associated liver disease, consider use of IV fat emulsion using nonsoybean sources to increase the omega-6 polyunsaturated fatty acid content. |

Table. Common clinical situations encountered by Nutrition Support Services.
Dr. McMahon notes: “Our service provides recommendations about whether nutrition support is indicated and, if so, which route — gastric or jejunal tube feeding or parenteral nutrition (PN) — is optimal. Subsequently, we recommend a nutrition program tailored to the patient and provide a metabolic monitoring program.

“One of our goals is to prevent or minimize the frequency of nutrition-related complications, such as unnecessary initiation of nutrition support or overfeeding. We follow the use of short-term PN (less than seven days) as a quality marker, as the expected benefits do not outweigh the risks to the patients for shorter use. Mandatory NSS consults are required for patients on medicine services prior to PN initiation. Subsequently, the percentage of short-term PN use has significantly decreased.

“Consults are also required before placement of a long-term tube feeding access. This approach ensures long-term feeding is appropriate for clinical and ethical situations and addresses reimbursement requirements, selects best tube and site (pre-pyloric or post-pyloric) for administration, and develops nutrition programs.”

Frequent consult requests on NSS include assessments for PN or long-term tube feeding in patients with complex medical and surgical histories, and evaluation and management of vitamin and mineral deficiencies. The NSS consultant reviews the patient’s medical and surgical history and labs, examines the patient, and with team members, develops the optimal nutrition and monitoring program. Dietitians provide expertise in specialized oral diets and tube feeding formulas. Nurses offer input on types of enteral tubes and site-care issues for nutrition-related tubes and catheters. Dietitians and nurses educate patients and caregivers on tube feeding administration post-hospital dismissal. They also work closely with the home enteral and home parenteral teams for patients dismissed on these therapies.

Dr. McMahon adds: “A current nursing focus is introducing the use of ENFit, a new connection device for enteral tubing. Enteral tubing misconnection occurs when enteral devices are connected to nonenteral devices, such as intravenous lines. To improve safety, this global initiative makes all tube feeding devices specific to tube feeding so that one can only use products designed for tube feeding access.

“Pharmacists provide expertise with PN program design, drug-nutrient interactions and drug shortage management. In addition, the dietitians, nurses and pharmacists play the key role of interfacing with clinicians of all disciplines regarding nutrition issues throughout the hospital campuses. Patients are assessed daily and the nutrition program is altered as needed.

“The multidisciplinary nature of the nutrition support service allows for a better educational experience for learners and ultimately better patient care.”
2019 Graduating Clinical Endocrinology Fellows

Maria (Daniela) D. Hurtado Andrade, M.D., Ph.D., Anupam Kotwal, M.B.B.S., and Tiffany M. Cortes, M.D., 2019 graduating Clinical Endocrinology fellows, and Kurt A. Kennel, M.D., program director, Clinical Endocrinology Fellowship at Mayo Clinic in Rochester, Minnesota. Dr. Hurtado Andrade’s new appointment is in Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic Health System — Franciscan Healthcare in La Crosse, Wisconsin, and Mayo Clinic in Rochester, Minnesota. Dr. Kotwal’s new appointment is in Diabetes, Endocrinology and Metabolism at the University of Nebraska Medical Center in Omaha, Nebraska. Dr. Cortes’ new appointment is with Endocrinology at the University of Texas Health Science Center at San Antonio.

2019 Graduating Endocrine Surgery Fellow

Megan G. Berger, M.D., 2019 graduating Endocrine Surgery fellow, and Melanie L. Lyden, M.D., program director, Comprehensive Endocrine Surgery Fellowship at Mayo Clinic in Rochester, Minnesota. Dr. Berger’s new appointment is with University of Minnesota Physicians at Fairview Ridges in Burnsville, Minnesota.

Education Opportunities

Endocrine Update 2020
Feb. 24-28, 2020, in San Juan, Puerto Rico

For more information or to register, visit https://ce.mayo.edu/endocrinology, call 800-323-2688 (toll-free) or email cme@mayo.edu.