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The clinical spectrum of McCune-Albright syndrome and its management

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Abstract

McCune-Albright Syndrome (MAS) is a rare, mosaic disorder presenting along a broad clinical spectrum. Disease arises from somatic activating *GNAS* mutations, leading to constitutive $G\alpha_s$ activation and ligand-independent signaling of the G_s-coupled protein receptor. The phenotype is largely determined by location and extent of tissues in which the *GNAS* mutation is expressed, as well as the pathophysiologic effects of $G\alpha_s$ activation within these tissues. Patient present clinically with a variable combination of fibrous dysplasia of bone (FD), café-au-lait skin macules, and hyperfunctioning endocrinopathies. In bone, $G\alpha_s$ leads to impaired differentiation of skeletal stem cells and formation of discrete, expansile FD lesions, resulting in fractures, pain, and functional impairment. A systematic approach to diagnosis and management is critically important to optimize outcomes for patients with FD/MAS. There are no medical therapies capable of altering the disease course in FD, however screening and treatment for endocrinopathies can mitigate some skeletal morbidities. This review summarizes current understanding of MAS pathophysiology, describes the spectrum of clinical features, and includes a detailed discussion of the recommended approach to diagnosis and management

Keywords

fibrous dysplasia; fibroblast growth factor 23; metabolic bone disease; $G\alpha_s$; mosaicism

Introduction

McCune-Albright Syndrome (MAS) is a rare mosaic disorder that presents along a broad clinical spectrum. MAS was originally described in 1936 as a triad of fibrous dysplasia of bone (FD), café-au-lait skin macules, and precocious puberty (1). However, it is now recognized that the phenotype is far more complex (2). The broad phenotypic spectrum can make MAS a challenging disorder for clinicians. However, taking a systematic approach that considers MAS in its context as a mosaic, multisystemic disorder can provide clarity in the diagnosis and management of this interesting disease.

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Pathogenesis

MAS arises from activating mutations in *GNAS,* which encodes the α-subunit of the G_s G-coupled protein receptor (3). These mutations lead to loss of the α-subunit's intrinsic GTPase activity, leading to constitutive receptor activation and inappropriate cAMP production. Arg201 is a key component of the GTPase and the most common site of pathogenic mutations (4). >95% of disease causing missense mutations occur equally at the R201H and R201C positions; uncommonly mutations may occur at Q227 and other positions (5).

Mutations in MAS are somatic, occurring early in embryogenesis. The resulting phenotype is determined largely by the extent and location of mutation-bearing tissue. Consistent with mosaic disease, MAS is not inherited, and there are no known cases of vertical transmission. There are no known genetic or environmental risk factors, and disease appears to occur in all ethnic groups (2).

Constitutive, ligand-independent signaling through the LH, FSH, TSH, GHRH, and ACTH receptors results in the hyperfunctioning endocrinopathies characteristic of MAS (3). In bone, constitutive $G\alpha_{s\alpha}$ activation impairs differentiation of skeletal stem cells, leading to replacement of normal bone and marrow with immature woven bone and fibrotic stroma (6) (Fig 1D&E).

Clinical Features

Fibrous Dysplasia

FD ranges from trivial monostotic disease affecting one bone, to debilitating polyostotic disease (7). FD lesions can occur in isolation or in combination with additional features of MAS.

Clinical sequelae of FD in the appendicular skeleton arises due to FD's tendency to fracture and deform under weight-bearing forces. Patients frequently present to care due to limp or pain (2). The proximal femur is one of the most commonly involved sites and may develop a characteristic coxa vara ("shepherd's crook") deformity (8) (Fig 1C). Fracture rates are highest during childhood and adolescence, and steadily decrease into adulthood (9), potentially related to increased FD activity in younger patients (discussed further below).

FD in the axial skeleton can result in scoliosis, which may be progressive and rarely lethal (10) (Fig 1B). Scoliosis is associated with hip malalignment and leg length discrepancy, which contribute to ambulation difficulties (11, 12).

Craniofacial FD typically presents with a slow-growing, painless swelling, which may result in facial asymmetry (2)(Fig 1A). Mild, asymptomatic craniofacial FD may be asymptomatic, and is often found incidentally on imaging studies such as dental radiographs and post-traumatic computed tomography scans (13). In rare and severe cases, patients may experience pain, paresthesia, or functional deficits, such as malocclusion, hearing impairment, and/or visual disturbances (13–16)(Fig 2E). Rarely, compression of the cerebellum and brainstem can develop in patients with skull base FD (17).

The natural history of FD includes typical age-related changes in disease progression and activity. *In utero* skeletal development appears to occur relatively normally, without obvious signs of FD at birth. FD lesions become apparent during early childhood and tend to progress in number and size until final skeletal burden is established by age 15 years (18). *In vitro* studies suggest that lesions eventually "burn out" during adulthood as the population of mutated skeletal stem cells depletes (19). Age-related changes in FD are also observed radiographically. Appendicular lesions typically have a homogenous, "ground glass" appearance on radiographs, which appear more heterogeneous and sclerotic changes with age (20). Craniofacial lesions tend to develop irregular, radiolucent-appearing areas on computed tomography over time (20).

Overproduction of fibroblast growth factor 23 (FGF23) from mutation-bearing skeletal stem cells is a key feature of FD (21). FGF23 is potent phosphate regulator, acting at the proximal renal tubule to decrease 1-α-hydroxylase activity and increase urinary phosphate excretion. Increased serum FGF23 and renal phosphate wasting are found commonly in patients with FD, however, frank hypophosphatemia is uncommon due to compensatory regulatory mechanisms (22, 23). Hypophosphatemia typically only develops in patients with a high skeletal disease burden and may wax and wane over time (21).

Skin

Café-au-lait macules are often the first clinically apparent manifestations of MAS, presenting at or shortly after birth (2). However, their significance is often noted only in retrospect, after other symptoms have developed. Café-au-lait macules have a characteristic appearance that includes jagged, irregular borders (often described as resembling the "coast of Maine"), and location respecting the midline of the body (5)(Fig 2A&C).

Gonadal involvement

Although MAS gonadal involvement occurs equally in girls and boys, overproduction of sex steroids is far more common in girls. In one large series of patients seen at the NIH, *GNAS* activation in ovarian tissue resulted in recurrent estrogen-producing cysts in approximately 85% of girls (5, 24)(Fig2A&B). Patients develop acute onset of pubertal signs, including breast development and growth acceleration. Labs show elevated estradiol levels with suppressed gonadotropins, and ultrasonography typically shows uterine enlargement with single or multiple ovarian cysts. Cyst resolution is associated with an acute drop in estradiol, which triggers vaginal bleeding. Between episodes girls are often clinically asymptomatic with undetectable estradiol levels and normal ultrasonographic findings, which may lead to delayed diagnoses. Ovarian torsion is an uncommon complication (25). Autonomous ovarian activity persists into adulthood and is commonly associated with menometorrhagia and fertility effects (25).

GNAS activation in the testes leads to Leydig and Sertoli cell hyperplasia, which presents clinically with macro-orchidism and ultrasonographic abnormalities, including focal masses, diffuse heterogeneity, and microlithiasis (26). Testicular volume is therefore an inaccurate indicator of precocious puberty in boys with MAS. While approximately 85% of boys have testicular involvement, only 15% develop autonomous testosterone production, which

presents with clinical signs of androgenization including public and axillary hair, penile enlargement, and growth acceleration (24, 26).

Secondary central puberty may develop as a complication of gonadotropin-independent puberty, typically at a bone age of 9 years or greater.

Thyroid

Thyroid abnormalities have been reported in approximately ~50% of patients with MAS, about half of whom develop frank hyperthyroidism (24, 27)(Fig2C&D). Clinical and ultrasonographic findings include diffuse enlargement, heterogeneity, and discrete cystic and solid nodules (27, 28). Biochemically, *GNAS* mutations result in constitutive 5'-deiodinase activity, resulting in increased conversion of T4 to T3 and a primary T3 toxicosis (28). Hyperthyroidism typically develops during childhood and persists throughout adulthood.

Pituitary

GNAS activation in the pituitary results in somatolactroph cell hyperplasia, leading to constitutive growth hormone (GH) and prolactin production in approximately 15% of patients (2, 24). The most common clinical sign is expansion of craniofacial FD, which is particularly sensitive to the effects of GH (29)(Fig2E&F). Symptoms may include progressive macrocephaly, vision loss, and hearing loss, all of which may signal the presence of GH secretion abnormalities, even in the absence of frankly elevated IGF-1 levels (14, 29). Other manifestations include growth acceleration, acromegalic features, and the development of secondary pituitary hormone insufficiencies (30). While growth acceleration and tall stature may suggest the presence of GH excess, this is not a consistent finding in patients with MAS because linear growth is often confounded by skeletal deformities and other endocrinopathies. GH excess is diagnosed by IGF-1, oral glucose tolerance test, and/or overnight GH sampling; most patients also demonstrate concomitant mild elevations in prolactin.

Neonatal Hypercortisolism

Hypercortisolism is one of the rarest and most serious complications of MAS (24). It arises due to *GNAS* activation in the fetal adrenal gland and presents exclusively during the first year of life (31, 32). Infants are often born small for gestational age and can develop failure to thrive, feeding problems, Cushingoid features, hypertension, respiratory disease, or other signs of illness (33). Symptoms can be insidious and non-specific, which may lead to delayed diagnoses (31). Adrenalectomy may be life-saving for severely affected patients, however medical therapy is an option for patients who are either mildly affected or too unstable for surgery. Hypercortisolism may spontaneously resolve in up to 1/3 of patients, likely due to involution of the fetal adrenal gland (31, 32). Long-term sequelae of neonatal hypercortisolism include neurodevelopmental effects (31) and late-onset adrenal insufficiency after spontaneous resolution (2).

Evaluation and Management

Diagnostic criteria

The diagnosis of MAS is most often made clinically, based on 2 or more characteristic features (Table 1) (2, 34). Mutation detection is variable and depends upon the level of mosaicism in the tissue being tested, and the sensitivity of the technique (2). PCR-based sequencing methods have mutation detection rates of greater than 80% in lesional tissue, and ~20–30% in peripheral blood lymphocytes (35–37). While detection of a pathogenic *GNAS* mutation may be helpful in establishing the diagnosis, a negative result does not rule out FD/MAS; mutation testing therefore does not typically affect management in patients with established clinical diagnoses.

Fibrous Dysplasia

By age 5 years, 90% of clinically significant FD can be identified in some form on bone scintigraphy; for this reason, a staging scintigraphy scan at this age is recommended for all patients with known or suspected FD/MAS (18, 34). Depending on the identified areas of involvement, additional imaging with radiographs or computed tomography may be indicated to better characterize individual lesions. No medical treatments have been shown to affect the quality or progression of FD lesions, therefore, clinical management focuses on optimizing function and mitigating risk factors that contribute to skeletal morbidity.

Management of appendicular FD focuses on correcting and preventing deformities and fractures (38). Proximal femoral (“shepherd’s crook”) deformities are particularly challenging, especially in young children where surgical options are limited by small size and skeletal growth (Fig 1C). Techniques commonly used in other conditions, such as curettage and grafting, have limited utility in patients with extensive FD involvement (39). Surgical approaches must therefore be individualized to account for the challenges and needs of each patient (38, 40).

Patients with craniofacial FD require a baseline head computed tomography scan to assess the affected structures (2, 34)(Fig 1A), and should undergo annual evaluations by a neuro-ophthalmologist and otolaryngologist to monitor for vision and hearing impairment (14, 29). Optic neuropathy is uncommon even in patients with FD involving the optic canals; prophylactic optic nerve decompression is therefore not indicated and has been associated with an increased risk of blindness (16, 41). Patients should be monitored for symptoms associated with cranial base deformities such as basilar invagination and Chiari I malformation (17). Consistent dental care should be prioritized for patients with FD affecting the teeth-bearing bones, who can uncommonly develop complications such as periodontal disease and malocclusion (13). Outcomes from craniofacial surgery are often unsatisfactory due to high risk of postoperative FD regrowth, particularly in patients with GH excess (42). Surgical indications should therefore be limited to correction of functional impairment and severe, disabling deformity.

Severe and progressive scoliosis can typically be managed with spinal fusion, which often shows favorable outcomes in FD (12). Regular physiatric care to optimize gait and

alignment, including orthoses to correct leg length discrepancies, is an important component of management that may mitigate progression of scoliosis and other deformities (11, 12).

Pain is a common feature in FD, affecting approximately 80% of patients (43). The occurrence and severity of FD pain appear to increase with age, counter to the typical age-related decrease in FD activity (44). Pain levels do not correlate with skeletal disease burden (44). FD pain can be treated medically with oral analgesic medications and supportive measures, and intravenous bisphosphonates may be helpful for patients with persistent, moderate to severe pain (34, 43). Despite their likely analgesic effects, bisphosphonates have not been demonstrated to improve bone quality or prevent FD lesion expansion (45–47). Concerningly, osteonecrosis of the jaw has been reported in association with bisphosphonate treatment in FD (48); therefore, it is recommended that bisphosphonates be limited to treatment of FD-related pain, using the lowest effective dose and interval (34).

Evaluation and treatment of MAS endocrinopathies (discussed below) is a key component of management in FD, because uncontrolled endocrinopathies contribute to skeletal morbidity. GH excess fuels craniofacial FD expansion, leading to increased risk for vision loss (29), hearing loss (14), and postoperative FD regrowth (42). Hypophosphatemia and hyperthyroidism increase risk of fractures, deformities, and pain, likely through metabolic effects that further decrease the mechanical stability of FD bone (9, 12, 14, 17). Patients with polyostotic FD should have serum phosphorus levels monitored regularly, with a low threshold for intervention with vitamin D analogues and phosphorus supplementation. Dosing is similar to X-linked hypophosphatemia, a more common disorder of FGF23 excess (49). Burosumab, a monoclonal antibody to FGF23 approved for treatment of X-linked hypophosphatemia, has not yet been studied in FD but holds promise as a potential therapy (50).

Endocrinopathies

All patients with MAS should be evaluated for endocrinopathies with a targeted history and physical exam, review of growth curve, and a bone age examination (2, 34). Gonadal evaluation should include screening testicular ultrasound in all boys, and in girls with findings suggestive of precocious puberty. Treatment should be aimed at mitigating negative effects of precocious puberty on psychosocial development and adult height. Girls can generally be managed with the aromatase inhibitor letrozole, which is effective in decreasing frequency of vaginal bleeding and improving final adult height (51). If letrozole monotherapy is ineffective, estrogen receptor modulators such as tamoxifen and fulvestrant may be considered (52, 53). Boys with precocious puberty are treated with testosterone receptor blockers, such as bicalutamide or spironolactone, used in combination with an aromatase inhibitor to prevent bone age advancement (26). Children may require GnRH agonists therapy in addition to these blocking agents for treatment of secondary central precocious puberty (26, 51). Management of menometorrhagia may include use of progestin-containing intrauterine devices or oral contraceptive pills (25). Pregnancy is likely achievable and safe in women with MAS, however ovarian disease may make conception more challenging, and clinicians should have a low threshold to refer patients desiring pregnancy to fertility specialists (25).

Hyperthyroidism typically responds to anti-thyroidal medications for short-term management. Most patients ultimately elect for definitive treatment, which is ideally achieved through thyroidectomy at an experienced, high-volume surgical center (2). Radioablation is also effective and may be preferred in patients who present surgical risks, or who don't have access to sufficiently experienced centers. However, clinicians should be aware of the theoretical risk of subtherapeutic radiation exposure to adjacent unaffected tissue given the patchy, mosaic nature of thyroid involvement (27, 34).

Patients with GH excess are typically treated medically with somatostatin analogues, used alone or in combination with GH receptor blockers (34, 54). Because craniofacial FD is particularly susceptible to the effects of GH, aggressive management is preferred, with the goal of decreasing IGF-1 between −2 and +1 standard deviations for children, and as low as possible for adults (2, 34, 54, 55). Hyperprolactinemia in MAS is typically mild, however patients with symptoms such as galactorrhea or central hypogonadism generally respond well to dopamine agonists such as cabergoline. Pituitary involvement is typically diffuse, even if discrete adenomas are visible on magnetic resonance imaging (54, 56). For this reason, surgical treatment typically requires total hypophysectomy, and is generally reserved for patients who are uncontrolled with maximal medical therapy. Surgery is often technically difficult due to FD involvement in the skull base (56). The presence of skull base FD also complicates radiation treatment, which has been associated with sarcomatous transformation in this area and should be reserved for final recourse in patients with severe, disabling disease (34, 54).

Other Manifestations

Gastrointestinal

MAS may be associated with a broad spectrum of gastrointestinal disease. Neonatal cholestasis and hepatitis has been reported in infants (57), and a variety of hepatobiliary abnormalities have been reported in adults, including hepatocellular adenomas, choledochal cysts, and inflammatory adenomas (58, 59). Gastric polyps may be asymptomatic or associated with symptoms of reflux (60, 61). Activating *GNAS* mutations are known drivers for the development intraductal papillary mucinous neoplasms (IPMNs) (62). These pancreatic cysts have been reported in up to 40% of patients with MAS and have rarely been associated with obstructive pancreatitis and diabetes (58, 60, 63). Gastrointestinal evaluation, including pancreatic imaging, should therefore be considered in all symptomatic patients (2,63). Although IPMNs are considered a potentially pre-malignant lesion in the general population, the risk of pancreatic adenocarcinoma in patients with MAS appears to be low, with only one reported case (64). It is unknown if IPMNs associated with MAS are truly at lower risk compared to the general population, or if the malignant potential of IPMNs is lower than previously thought (65).

Bone marrow and hematologic

Bone marrow failure with pancytopenia and extramedullary hematopoiesis has been rarely reported in patients with severe FD (66, 67). The etiology is not well-established but may be related to reduced marrow capacity in conjunction with splenic sequestration, and patients

have clinically improved after splenectomy (66, 67). Platelet dysfunction has also been reported in association with MAS (68), which together with the hypervascularity of FD lesions, may contribute to blood loss with orthopedic procedures.

Malignancy

GNAS mutations are weak oncogenes, and in the general population have been associated with thyroid adenomas, pituitary adenomas, and intraductal papillary mucinous neoplasms (69). An increased risk of breast cancer has been identified in patients with MAS, and early screening with mammography is recommended for patients with polyostotic FD and ovarian involvement (70). Malignant transformation of FD has also been reported, particularly in patients exposed to external beam radiation (54, 71). Patients typically present with new-onset pain and/or rapid expansion in a previously inactive lesion, which radiographically may show expansion through the bony cortex. This should be distinguished from fluid-filled aneurysmal bone cysts, which also arise acutely and expand rapidly within FD bone. The prevalence of malignant transformation in FD has not been determined, however it is likely low and has been observed in only 2/250 patients in the NIH cohort (unpublished observation, AMB & MTC). Other malignancies reported in association with MAS include thyroid (72), testicular (26), pancreatic (64), and hepatoblastoma (57).

Future Directions

Identifying treatments capable of altering FD lesion activity is a high priority for clinical and translational research. The recent development of several mouse models represents an important advance that may be used to identify and test novel therapeutic targets (73–75). Another ongoing strategy is high throughput screening to identify molecules with activity at the mutant G_s-receptor (76). Recent evidence suggests denosumab, a monoclonal antibody to receptor activator of nuclear-B kappa ligand, may be effective in treating pain and slowing FD lesion expansion (77, 78). However, concerningly, denosumab discontinuation has been associated with severe, life-threatening hypercalcemia in patients with FD (77), and further research is needed to determine if and how denosumab can be used safely in this population.

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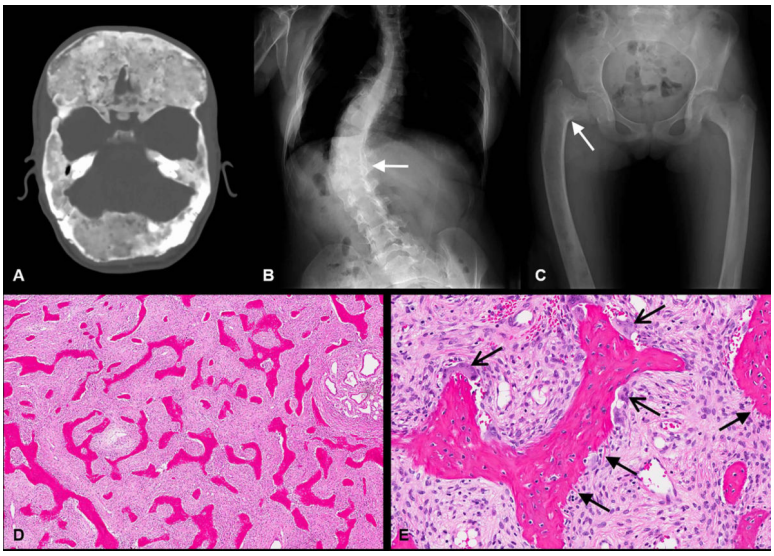

Figure 1. Radiographic and histologic features of fibrous dysplasia (FD).

(A) Axial CT with diffuse skull base FD. Note the characteristic homogeneous, “ground glass” appearance of FD bone. (B) Radiograph of the spine with scoliosis secondary to vertebral FD (white arrow). (C) Femoral FD with a classic varus (“shepherd’s crook”) deformity (white arrow). (D, E) FD histology: H&E stain demonstrating classic curvilinear trabeculae and hypercellular fibrous stroma; (D) low power view and (E) high power view demonstrating signs of increased remodeling including Sharpey fibers (open arrows) and abundant osteoclasts (closed arrows).

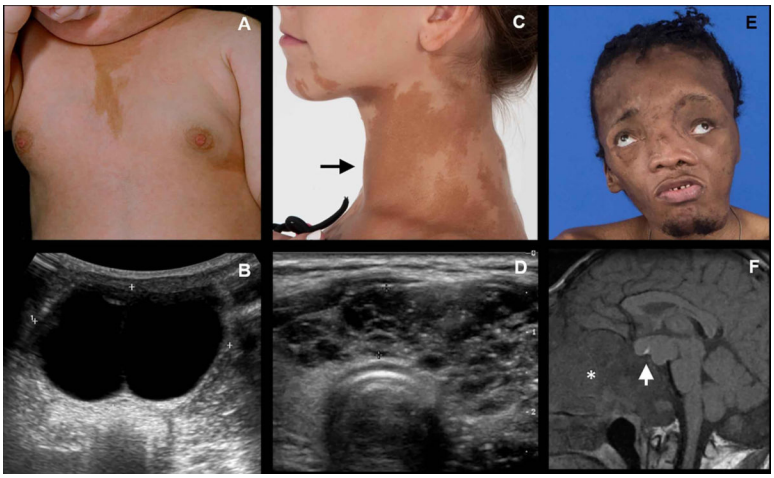

Figure 2. Clinical and radiographic features of McCune-Albright Syndrome (MAS).

(A) An infant with a typical appearing café-au-lait macule and breast budding; (B) corresponding pelvic ultrasound shows a large estrogen-producing ovarian cyst. (C) Adolescent with typical appearing café-au-lait macules affecting her neck and jaw, and a goiter (arrow) consistent with hyperthyroidism; (D) corresponding thyroid ultrasound demonstrating an abnormal, heterogenous cystic gland. (E) Patient with uncontrolled growth hormone excess resulting in macrocephaly and vision loss; (F) T1-weighted MRI with large growth hormone-secreting pituitary adenoma (arrow) and thickened cranial base secondary to fibrous dysplasia.

Table 1.

Diagnostic criteria for fibrous dysplasia/McCune-Albright syndrome[1]

• Fibrous dysplasia of bone[2]
• Café-au-lait skin pigmentation with characteristic features[3]
• Gonadotropin-independent precocious puberty resulting from recurrent ovarian cysts in girls and autonomous testosterone production in boys
• Testicular lesions with or without associated gonadotropin-independent precocious puberty
• Thyroid lesions with or without non-autoimmune hyperthyroidism
• Growth hormone excess
• Neonatal hypercortisolism

[1] Two or more clinical features are consistent with the diagnosis of FD/MAS.

[2] The presence of an isolated monostotic lesion in the absence of extraskeletal features requires a biopsy for diagnostic certainty.

[3] Hyperpigmentation with irregular borders, distribution reflecting the midline of the body.

Table 2.

Medications commonly used in treatment of McCune-Albright syndrome

Indication	Medication	Mechanism of action	Potential adverse effects
Precocious puberty	Letrozole	Aromatase inhibitor	Transient transaminemia
	Tamoxifen	Estrogen receptor modulator	Endometrial hyperplasia
Hyperthyroidism	Methimazole	Thyroperoxidase inhibitor	Hepatotoxicity, agranulocytosis
	Propylthiouracil	Inhibits thyroperoxidase and 5'-deiodinase	Hepatotoxicity, agranulocytosis
Growth hormone excess	Octreotide; Lanreotide	Somatostatin analog	Cholelithiasis, hepatotoxicity
	Pegvisomant	Growth hormone receptor antagonist	Hepatotoxicity
Neonatal hypercortisolism	Metyrapone	11-beta-hydroxylase inhibitor	Hirsutism, hypertension, hyperkalemia
	Ketoconazole	Inhibits cortisol synthesis	Hepatotoxicity, hypogonadism
FGF23-mediated hypophosphatemia	Calcitriol; Alfacalcidiol	Increases dietary calcium absorption and renal tubular calcium reabsorption	Hypercalciuria, hypercalcemia
	Phosphorus	Supplemental	Gastrointestinal effects