WebLog Journal of Endocrinology and Diabetes

Case Report
Published: 15 Jun, 2026

A Rare Presentation of McCune–Albright Syndrome in a Nine-Year-Old Boy with Giant Craniofacial Polyostotic Fibrous Dysplasia, Café-au-Lait Macules, and Precocious Puberty

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Received Date: *10 May 2026*
Accepted Date: *13 Jun 2026*
Published Date: *15 Jun 2026*

Citation:
Khatri LK, Endeley EML, Swamy KB, Bhattacharya DC, Correia RC, Mehta AR, et al. A Rare Presentation of McCune–Albright Syndrome in a Nine-Year-Old Boy with Giant Craniofacial Polyostotic Fibrous Dysplasia, Café-au-Lait Macules, and Precocious Puberty. WebLog J Endocrinol Diabetes. wjed.2026.f1502. https://doi.org/10.5281/zenodo.20965691

ISSN 3071-3986

Abstract

Background: McCune–Albright syndrome (MAS) is a rare mosaic disorder classically defined by the triad of polyostotic fibrous dysplasia, café au lait macules, and endocrine hyperfunction. The full triad is uncommon, and presentation in males is particularly rare.

Case: We report a nine-year-old boy presenting with progressive craniofacial deformity, multiple café au lait macules, and signs of precocious puberty. Imaging revealed extensive expansile polyostotic fibrous dysplasia involving the cranial vault and facial bones. Endocrine evaluation confirmed gonadotropin independent precocious puberty. Genetic testing identified an activating GNAS mutation consistent with MAS.

Conclusion: This case represents a rare, classical triad presentation of MAS in a male child, with unusually extensive craniofacial involvement. Early recognition and multidisciplinary management are essential to prevent functional compromise and optimise long term outcomes.

Keywords: McCune–Albright Syndrome (MAS); Polyostotic Fibrous Dysplasia (PFD); Craniofacial Fibrous Dysplasia; Precocious Puberty; Café-au-Lait Macules; GNAS Gene Mutation; Gαs Protein Activation; Pediatric Endocrinology; Rare Diseases

Introduction

McCune–Albright Syndrome (MAS) is a rare, complex multisystem disorder classically defined by a triad of polyostotic fibrous dysplasia (PFD), café-au-lait macules, and precocious puberty (PP). The earliest descriptions of the condition were provided by McCune in 1936 [1] and Albright et al. in 1937 [2], followed by the foundational pathological characterisation by Lichtenstein and Jaffe in 1942 [3].

While MAS is more frequently diagnosed in females, its presentation in males often includes unique endocrine challenges and severe skeletal involvement. MAS is a sporadic, non-inherited disorder caused by post-zygotic activating mutations in the GNAS gene, leading to constitutive activation of Gsα and excess cAMP signalling [4]. The clinical phenotype depends on the distribution of mutated cells and may include fibrous dysplasia (FD), café-au-lait macules, and endocrine hyperfunction.

The full triad is rare, and presentation in boys is particularly uncommon. Craniofacial FD can be severe, causing deformity, visual impairment, airway obstruction, and psychosocial burden.

Contemporary guidelines emphasise the complexity of craniofacial FD and the need for structured evaluation and monitoring [5, 6].

We present a once-in-a-lifetime case of a nine-year-old boy with the complete MAS triad and massive craniofacial polyostotic FD leading to significant cranial deformity, asymmetry, and risk of sensory impairment.

Case Presentation

A nine-year-old boy presented with progressive facial asymmetry, frontal bossing, and intermittent headaches over two years. Patient was referred for evaluation of progressive craniofacial asymmetry with multiple giant bumps on the head, and early signs of secondary sexual characteristics. His parents noted a painless "lump" on his forehead and right cheek that had gradually enlarged over three years, Parents reported rapid growth, acne, and behavioural changes suggestive of early puberty. There was no family history of endocrine or skeletal disorders.

Physical examination revealed marked craniofacial asymmetry with bony expansion of the maxilla, mandible, frontal and sphenoid bones, multiple large café-au-lait macules with irregular "coast-of-Maine" borders pattern on the trunk, neck and back, testicular enlargement and pubic hair consistent with Tanner stage III and normal neurological examination.

Diagnostic Investigations

Imaging Findings

Skeletal Survey: Whole-body scintigraphy identified multiple other FD lesions in the right femur and ribs, confirming the polyostotic nature of the disease.

CT and MRI of the skull demonstrated extensive **expansile intramedullary lesions** with classic "ground-glass" matrix, involvement of the frontal, sphenoid, maxillary, zygomatic, and temporal bones, cortical thinning without periosteal reaction, narrowing of the orbital apex and ethmoid sinuses and no intracranial extension.

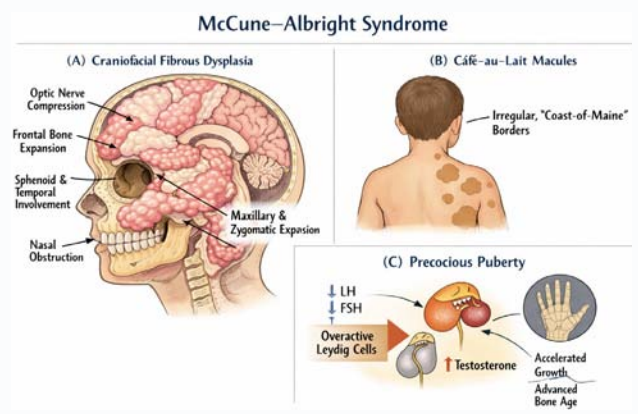

Figure 1: Composite schematic of McCune–Albright syndrome in a 9-year-old boy.
(A) Craniofacial polyostotic fibrous dysplasia showing expansile fibro-osseous lesions with ground-glass matrix and optic nerve compression.
(B) Café-au-lait macules with irregular "coast-of-Maine" borders.
(C) Endocrine pathway of gonadotropin-independent precocious puberty illustrating autonomous testosterone production, suppressed gonadotropins, and accelerated skeletal maturation.
Together, these panels depict the triad of fibrous dysplasia, cutaneous pigmentation, and endocrine hyperfunction characteristic of McCune–Albright syndrome.

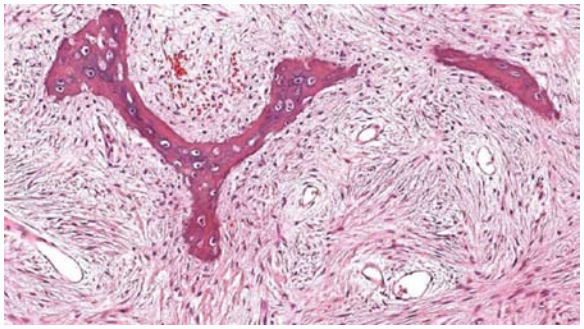

Figure 2: Histopathology of Fibrous Dysplasia ("Chinese-Letter" Trabeculae)
Histological schematic illustrating the classic microscopic features of **fibrous dysplasia**. The section shows **irregular, curvilinear woven bone trabeculae** arranged in a characteristic *"Chinese-letter"* pattern, embedded within a **moderately cellular fibrous stroma** composed of spindle-shaped fibroblasts and delicate collagen fibres. The trabeculae are **devoid of osteoblastic rimming**, distinguishing fibrous dysplasia from ossifying fibroma and other fibro-osseous lesions. The intervening stroma demonstrates variable vascularity and absence of inflammatory infiltrate. These features represent the hallmark fibro-osseous architecture produced by the **post-zygotic activating *GNAS* mutation** in **McCune–Albright syndrome**.

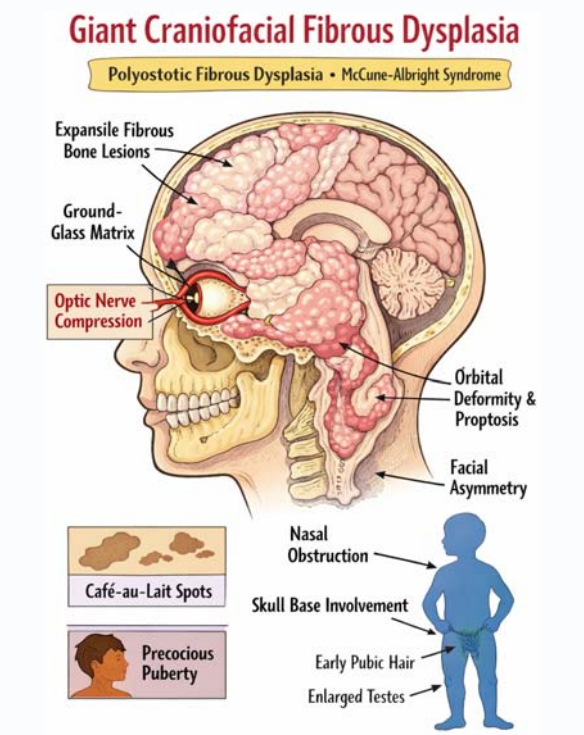

Figure 3: Giant Craniofacial Fibrous Dysplasia in McCune–Albright Syndrome
Composite schematic illustrating the anatomical and systemic manifestations of polyostotic fibrous dysplasia associated with McCune–Albright syndrome. The sagittal cranial section shows expansile fibrous bone lesions with a characteristic ground-glass matrix, involving the frontal, sphenoid, maxillary, and temporal bones. Arrows indicate optic nerve compression, orbital deformity and proptosis, nasal obstruction, and skull-base involvement, all contributing to craniofacial asymmetry.
Inset panels depict café-au-lait macules with irregular "coast-of-Maine" borders and precocious puberty features (early pubic hair and testicular enlargement), representing the endocrine component of the syndrome. Together, these findings demonstrate the triad of fibrous dysplasia, cutaneous pigmentation, and endocrine hyperfunction characteristic of McCune–Albright Syndrome.

Table 1: Differential Diagnosis of Craniofacial Fibro-Osseous Lesions.

Condition	Key Clinical Features	Radiological Features	Histopathology	Distinguishing Points
Fibrous Dysplasia (FD)	Painless swelling, deformity; may cause visual/dental issues; part of MAS	"Ground-glass" matrix; intramedullary expansion; cortical thinning; no periosteal reaction	Irregular woven bone ("Chinese characters") in fibrous stroma	Often polyostotic; associated with *GNAS* mutation; asymmetric
Ossifying Fibroma	Slow-growing, well-circumscribed jaw lesion; adolescents/young adults	Well-defined, expansile, mixed radiolucent–radiopaque; sclerotic rim	Fibrous stroma with cementum-like ossicles	Sharply demarcated (unlike FD); true neoplasm
Juvenile Ossifying Fibroma (JOF)	Rapid growth; aggressive; children <15 yrs	Expansile, destructive; "soap-bubble" appearance	Trabecular or psammomatoid ossicles	More aggressive; recurrence common
Paget Disease (rare in children)	Bone pain, deformity; extremely rare in paediatrics	Cortical thickening, coarse trabeculae, "cotton wool" skull	Mosaic lamellar bone	Age is key — almost never seen in children
Osteofibrous Dysplasia	Tibia/fibula predilection; rare in craniofacial bones	Cortical lucencies; anterior tibial bowing	Fibrous stroma with woven bone	Location distinguishes it
Chronic Osteomyelitis (sclerosing)	Pain, fever, sinus tracts	Mixed sclerosis/lysis; sequestrum/ involucrum	Chronic inflammatory infiltrate	Systemic signs; infection markers
Low-grade Osteosarcoma	Pain, swelling; rare in skull	Ill-defined margins; cortical destruction; soft-tissue mass	Malignant osteoid	Aggressive features; periosteal reaction
Cemento-Osseous Dysplasia	Middle-aged females; mandible	Radiolucent → mixed → radiopaque maturation	Cementum-like deposits	Demographic and jaw-only involvement

Table 2: Management Algorithm for McCune–Albright Syndrome (MAS) in Children.

Step 1 — Initial Clinical Recognition

- Craniofacial deformity.
- Café-au-lait macules (irregular borders, midline-respecting).
- Signs of endocrine hyperfunction (precocious puberty, hyperthyroidism, GH excess, Cushing's, phosphate wasting).

→ **If ≥1 feature present, proceed to full MAS evaluation**

Step 2 — Baseline Investigations

A. Imaging

- **CT/MRI of skull and face** → assess FD extent, optic canal, sinuses.
- **Skeletal survey or whole-body MRI** → detect polyostotic involvement.
- **DXA** (baseline bone density).

B. Endocrine Panel

- Testosterone/estradiol.
- LH/FSH.
- Thyroid function (TSH, fT4).
- IGF-1.
- Cortisol (AM, DST if needed).
- Serum phosphate, ALP.
- Vitamin D, PTH.

C. Genetic Testing

- Targeted *GNAS* mutation analysis (blood or tissue).

Step 3 — Diagnose and Classify

- **MAS confirmed** if:

1. *GNAS* mutation **OR**
2. ≥2 classical features (FD + café-au-lait + endocrine hyperfunction).

- **Classify FD**:

1. Monostotic.
2. Polyostotic.
3. Craniofacial dominant.
4. MAS-associated FD.

Step 4 — Endocrine Management

Precocious Puberty

- Boys: **Letrozole** or **Anastrozole.**
- Girls: **Aromatase inhibitors** ± **GnRH analogues** if central activation develops.
- Monitor bone age every 6–12 months.

Hyperthyroidism

- **Methimazole** first-line.
- Avoid radioiodine in children if possible.

GH Excess

- **Pegvisomant** or **Somatostatin analogues.**
- GH excess accelerates FD progression — treat aggressively.

Cushing's Syndrome

- Rare but severe → urgent endocrine referral.

Hypophosphatemia

- Oral phosphate + calcitriol.
- Monitor for nephrocalcinosis.

Step 5 — Craniofacial Fibrous Dysplasia Management

Indications for urgent intervention

- Optic nerve compression.
- Airway compromise.
- Severe deformity.
- Rapid expansion.
- Recurrent sinus obstruction.

Medical therapy

- **Bisphosphonates** for bone pain.

No evidence they halt lesion growth, but improve quality of life.

Surgical management

- **Contour surgery** once growth stabilises.
- **Decompression** for optic canal compromise.
- Avoid repeated curettage — lesions regrow.

Monitoring

- Annual ophthalmology review.
- CT/MRI every 1–2 years depending on severity.

Step 6 — Long-Term Follow-Up

- Multidisciplinary team: endocrinology, maxillofacial, neurosurgery, ophthalmology, orthopaedics, psychology.

- Annual endocrine panel.
- Growth and puberty monitoring.
- Psychosocial support (craniofacial involvement is high-impact).

Step 7 — Family Counselling

- MAS is **non-inherited.**
- Caused by **post-zygotic mosaic *GNAS* mutation.**
- No increased recurrence risk in siblings.
- Explain variability and long-term expectations.

Table 3: Key Management Considerations.
Management of this complex presentation requires a multidisciplinary team, including endocrinologists and craniofacial surgeons [1, 2].

Feature [1, 2, 4, 5]	Primary Management Approach
Precocious Puberty	Targeted medical therapy (e.g., aromatase inhibitors or antiandrogens) to block testosterone effects and preserve adult height potential.
Craniofacial PFD	Routine monitoring for vision and hearing changes. Surgical contouring is generally postponed until skeletal maturity unless function is compromised.
Growth Hormone	Aggressive screening for **growth hormone excess** is vital, as it can significantly drive the rapid expansion of craniofacial lesions.
Bone Health	**Bisphosphonates** (like pamidronate) or denosumab may be considered specifically for the management of bone pain or fragility.

The underlying cause is a sporadic, post-zygotic mutation in the **GNAS gene**, which results in mosaic activation of the Gsα protein. Because it is a somatic mutation, it is not an inherited condition [1-3].

These findings were consistent with **polyostotic craniofacial fibrous dysplasia**.

Endocrine Evaluation

Endocrine Findings: Pubertal assessment showed bilateral testicular enlargement (volume >4 mL) and increased penile length, consistent with precocious puberty. Laboratory results showed elevated testosterone with **suppressed LH/FSH**, confirming **gonadotropin-independent precocious puberty**, normal thyroid function, normal cortisol and IGF-1 and normal serum phosphate Bone age was advanced by 2.5 years.

Genetic Analysis

Targeted molecular testing of peripheral blood identified a **somatic activating mutation in *GNAS*** (c.601C>T; p.Arg201Cys), confirming the diagnosis of **McCune–Albright syndrome**.

Management

The child was managed by a multidisciplinary team including endocrinology, maxillofacial surgery, neurosurgery, ophthalmology, and psychology.

Interventions included: Endocrine Treatment: The patient was started on medications to suppress precocious puberty and prevent premature epiphyseal closure, which could lead to short adult stature.

- **Letrozole** for peripheral precocious puberty.
- **Bisphosphonate therapy** for bone pain and FD progression control.
- **Ophthalmology surveillance** for optic nerve compression.
- **Maxillofacial surgical planning** for future contouring once growth stabilises.

Surgical Management and Follow-up

Management required an interprofessional approach involving pediatric surgery, maxillofacial/plastic surgical, head and neck surgical (ENT), endocrinology, neurosurgery, and ophthalmology teams.

Surgical Intervention: Due to the "giant" nature of the craniofacial lesions and potential future optic nerve compression later, the patient underwent a successful surgical decompression to preserve visual function. Surgical management for giant craniofacial fibrous dysplasia (CFD) in McCune–Albright Syndrome (MAS) is complex, primarily due to the expansive, vascular nature of the dysplastic bone and its proximity to critical structures like the optic nerve and carotid arteries. Debulking and Recontouring For "giant" lesions causing significant facial asymmetry, conservative approaches are often preferred to radical resection to minimize morbidity.

Boney Recontouring (Shaving/Abrasion): The surgeon "shaves" the outer layers of the dysplastic bone using high-speed burrs to restore facial symmetry and improve aesthetics.

Long-term Monitoring: Regular follow-up with the NIH FD/MAS Alliance guidelines is requested and is essential to monitor for further skeletal complications, such as pathological fractures or other endocrine hyperfunctions like hyperthyroidism or growth hormone excess.

Discussion

MAS is a mosaic disorder with highly variable expression. The classical triad is uncommon, and male presentation with severe craniofacial FD is exceptionally rare. Craniofacial FD can be disfiguring and functionally debilitating due to optic canal narrowing, sinus obstruction, and dental malocclusion. These features were recognised in early descriptions of the disease [1–3] and remain central to modern diagnostic frameworks [4–7].

Precocious puberty is the most common endocrine manifestation in girls but is rare in boys. When present, it is typically severe and rapidly progressive, as in this case. Recent clinical series and genetic studies continue to highlight the variability of endocrine involvement in MAS and the importance of identifying GNAS mosaicism [8–10].

Diagnosis relies on clinical features, imaging, and confirmation of GNAS mutation. Management is supportive and multidisciplinary, focusing on endocrine control, prevention of functional compromise, and psychosocial support. Current best-practice guidelines emphasise the need for coordinated care across endocrinology, orthopaedics, ophthalmology, and craniofacial surgery [6, 7].

This case highlights the importance of early recognition of MAS in children presenting with craniofacial deformity and café-au-lait macules, even in the absence of classic endocrine symptoms. In boys with MAS, precocious puberty is primarily gonadotropin-independent, driven by autonomous testicular testosterone production rather than central activation [9].

Pharmacological protocols focus on androgen blockade and aromatase inhibition to prevent rapid bone maturation and premature epiphyseal closure [9, 10]. Transition to central precocious puberty may occur over time, requiring GnRH analogue therapy [9].

1. Combination Therapy (Standard Approach) [1]

The most common strategy involves a "dual blockade" to slow

physical virilization and prevent the premature closure of growth plates (epiphyses), which would otherwise lead to short adult stature [1].

- **Androgen Receptor Blockers:** These medications prevent testosterone from acting on tissues.

1. **Spironolactone:** Traditionally used to block androgen receptors.
2. **Bicalutamide:** A newer, non-steroidal anti-androgen increasingly used due to its once-daily dosing and potent effect [1-5].

- **Aromatase Inhibitors (AIs):** These block the conversion of androgens into oestrogen, the primary driver of advanced bone age.

1. **Letrozole or Anastrozole:** Third-generation AIs are the current preference due to high potency.
2. **Testolactone:** An older, first-generation AI that required multiple daily doses and is less frequently used today [1-5].

2. Alternative Steroidogenesis Inhibitors

If combination therapy is not feasible, medications that directly stop the production of hormones may be used.

- **Ketoconazole:** An antifungal that, in high doses, inhibits several enzymes involved in steroid synthesis. While effective at lowering testosterone levels, it carries a significant risk of hepatotoxicity (liver damage) and adrenal insufficiency, requiring strict monitoring [1-4].

3. Transition to Central Precocious Puberty [1]

A critical phase in MAS is when prolonged exposure to sex steroids "awakens" the brain's pubertal centre, leading to secondary gonadotropin-dependent (central) precocious puberty [1, 2].

- **GnRH Analogues:** If the patient develops elevated LH and FSH levels, medications like leuprolide acetate or triptorelin are added to the existing protocol to suppress the central axis [1, 2].

4. Monitoring and Goals

Treatment success is monitored through regular assessments of:

- **Growth Velocity:** Aiming for a normal prepubertal rate.
- **Bone Age:** Monitored *via* X-rays to ensure skeletal maturation is not outpacing chronological age.
- **Hormone Levels:** Serial tracking of testosterone and oestradiol to ensure adequate suppression [1-5].

Learning points and take-home messages:

The following learning points summarise the clinical pearls and diagnostic priorities for managing a complex presentation of McCune–Albright Syndrome (MAS) in a male patient:

1. Recognition of the Classic Triad

- **The "Coast of Maine":** Café-au-lait spots in MAS are typically large, unilateral, and have jagged borders. Their presence should immediately prompt a skeletal survey and endocrine screening, even if the patient is asymptomatic.
- **Male Presentation:** While MAS is rarer in boys, precocious puberty often manifests as autonomous testicular enlargement. Clinicians must distinguish this from central puberty by checking for suppressed gonadotropins (LH/FSH).

2. Monitoring Craniofacial Risks

- **Functional over Aesthetic:** In giant craniofacial FD, the primary goal of surgery is the preservation of sensory function (vision and hearing) rather than purely cosmetic correction.
- **The "Silent" Threat:** Optic nerve compression can be asymptomatic until significant vision loss occurs. Annual ophthalmological exams and high-resolution CT scans are mandatory for patients with sphenoid bone involvement.

3. Comprehensive Endocrine Screening

- **Growth Hormone (GH) Excess:** Up to 20% of MAS patients develop GH excess (acromegaly/gigantism). This is a critical learning point because untreated GH excess significantly accelerates the expansion of fibrous dysplasia lesions, particularly in the skull.
- **Phosphate Wasting:** Fibrous dysplasia lesions can produce the hormone FGF23, leading to renal phosphate wasting and rickets/osteomalacia, which further weakens the skeleton.

4. Conservative Surgical Philosophy

- **Stability over Radicality:** Dysplastic bone is highly vascular and prone to regrowth. Radical resection is often avoided in growing children in favour of conservative "shaving" or "debulking" to manage symptoms and symmetry while minimising surgical morbidity.

5. Multidisciplinary Life-long Care

- **Somatic Mosaicism:** Because MAS is caused by a post-zygotic mutation, the severity depends on which tissues are affected. Care must be coordinated between endocrinology, orthopaedics, ophthalmology, and radiology throughout the patient's life to manage new or progressing lesions.

Conclusion

This case highlights the importance of early recognition of the MAS triad in males. Giant craniofacial involvement in pediatric patients necessitates urgent imaging to assess for sensory nerve compression and comprehensive endocrine screening to manage precocious puberty and its systemic effects. We report a rare case of a nine-year-old boy with the full triad of McCune–Albright syndrome and massive craniofacial polyostotic fibrous dysplasia. This case underscores the need for high clinical suspicion, early endocrine evaluation, and coordinated multidisciplinary care to optimise outcomes in this complex disorder.

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