

Case Report

Hypocalcaemia Across the Adult Lifespan: Divergent Etiologies, Organ System Vulnerability, and Irreversible Sequelae – A Case Series

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Abstract

Hypocalcaemia is a common biochemical finding that rarely receives clinical attention beyond acute intravenous or oral replacement [1,2]. However, its downstream systemic manifestations vary widely depending on underlying pathophysiology, chronicity, the calcium-phosphate (Ca $\times$ P) product, and ambient parathyroid hormone (PTH) dynamics [1,3]. We describe three distinct presentations across the adult lifespan: (1) severe vitamin D deficiency and osteomalacia complicated by acute necrotizing pancreatitis; (2) idiopathic primary hypoparathyroidism with extensive neurocognitive and cerebellar manifestations secondary to bilateral basal ganglia calcification; and (3) neglected post-thyroidectomy hypoparathyroidism culminating in irreversible Fahr syndrome decades after surgery. This series highlights that hypocalcaemia is a multi-system metabolic disorder rather than an isolated biochemical target, where delayed etiological characterization leads to permanent structural and neurological damage [2,4].

INTRODUCTION

Disorders of calcium homeostasis are frequently reduced to numeric thresholds requiring reactive repletion [4,5]. Yet, calcium ions (Ca²⁺) serve as vital secondary messengers across excitable membranes, secretory epithelium, and skeletal matrices [1,6]. While neuromuscular tetany and prolonged QTc intervals represent the classic clinical triad, unbuffered mineral imbalances precipitate far more destructive phenotypes, including acute enzymatic auto-digestion of visceral organs and permanent intracranial mineral deposition [3,6,7].

The phenotypic trajectory of hypocalcaemia is dictated by four distinct variables:

1. **The underlying biochemical axis** (secondary hyperparathyroidism vs. primary parathyroid failure) [1,3]
2. **The calcium-phosphate product** (Ca $\times$ P) [2,8]
3. **The rate of onset versus chronicity** [3,5]
4. **End-organ tissue vulnerability across the lifespan** [9,10]

We report three illustrative cases highlighting the clinical divergence of hypocalcaemia, emphasizing diagnostic pitfalls and the necessity of proactive long-term surveillance.

Case Presentations

Case 1: Severe Nutritional Osteomalacia Associated with Acute Necrotizing Pancreatitis

A 38-year-old female presented with a 48-hour history of severe epigastric pain radiating to the back, persistent vomiting, and abdominal distension. Contrast-enhanced computed tomography (CECT) of the abdomen demonstrated acute necrotizing pancreatitis involving >30% of the pancreatic parenchyma, accompanied by extensive peripancreatic fluid collections (Modified CT Severity Index: 6/10). Extensive evaluation excluded common triggers: transabdominal ultrasonography and magnetic resonance cholangiopancreatography (MRCP) showed no cholelithiasis or choledocholithiasis; alcohol intake was absent; serum triglycerides were 118 mg/dL; and serum IgG4 levels were normal.

Initial laboratory evaluation revealed marked hypocalcaemia:

- Corrected serum calcium: **6.2 mg/dL** (Reference: 8.5–10.2 mg/dL)
- Serum inorganic phosphorus: **2.1 mg/dL** (Reference: 2.5–4.5 mg/dL)
- Serum magnesium: **1.9 mg/dL** (Reference: 1.7–2.4 mg/dL)
- Serum lipase: **1,420 U/L** (Reference: 10–140 U/L)
- 25-hydroxyvitamin D: **< 6.0 ng/mL** (Deficiency: < 20 ng/mL)
- Intact PTH (iPTH): **284 pg/mL** (Reference: 15–65 pg/mL)
- Total alkaline phosphatase: **412 U/L** (Reference: 44–147 U/L)

Skeletal radiographs revealed diffuse cortical thinning, generalized osteopenia, and pseudo-fractures (Looser zones) along the pubic rami, confirming profound nutritional osteomalacia with secondary hyperparathyroidism.

Although severe pancreatitis itself promotes calcium sequestration via peripancreatic fat saponification [7], the baseline biochemical footprint (severe chronic vitamin D deficiency, low baseline phosphate, and secondary hyperparathyroidism) pointed to preexisting metabolic bone disease as an independent cofactor [6,11]. Intensive supportive care, intravenous calcium gluconate infusions, followed by oral high-dose cholecalciferol (60,000 IU/week) and elemental calcium (1,500 mg/day) led to resolution of systemic inflammation, stabilization of calcium levels, and recovery without recurrent episodes.

Case 2: Idiopathic Primary Hypoparathyroidism Presenting as Neuropsychiatric Deterioration

A 36-year-old male with no prior medical history presented with progressive cognitive slowing, intermittent limb paresthesias, generalized tonic-clonic seizures, and depressive symptoms refractory to psychiatric pharmacotherapy. Neurological examination elicited positive Chvostek and Trousseau signs, mild bilateral dysidiadochokinesia, and extrapyramidal rigidity.

Laboratory evaluation demonstrated:

- Corrected serum calcium: **5.8 mg/dL**
- Serum inorganic phosphorus: **6.4 mg/dL**
- Serum magnesium: **2.0 mg/dL**
- Serum intact PTH: **4.2 pg/mL** (inappropriately low in the setting of marked hypocalcaemia)
- 25-hydroxyvitamin D: **32.4 ng/mL**

- 24-hour urinary calcium excretion: **42 mg/day** (low)

Non-contrast CT of the brain revealed extensive, symmetrical hyperdensities consistent with calcification in the globus pallidus, putamen, caudate nuclei, and cerebellar dentate nuclei [8,12].

A diagnosis of idiopathic primary hypoparathyroidism with secondary intracranial calcification was established [8,13]. The patient was started on calcitriol (0.5 mcg twice daily) and oral calcium carbonate (2,000 mg/day elemental calcium divided across meals) [1,2]. Over six months, serum calcium stabilized within the target low-normal range (8.0–8.5 mg/dL), achieving complete cessation of seizures and marked resolution of depressive symptoms. Repeat neuroimaging showed persistent, unchanged intracranial calcifications.

Case 3: Neglected Post-Thyroidectomy Hypoparathyroidism Leading to Fahr Syndrome

A 62-year-old female presented with progressive cognitive decline, gait ataxia, tremors, sleep fragmentation, and paroxysmal palpitations. She had undergone a total thyroidectomy for non-toxic multinodular goiter 18 years prior, but was lost to follow-up, maintaining only irregular levothyroxine substitution without calcium monitoring [9,14]. Laboratory investigation revealed:

- Corrected serum calcium: **6.1 mg/dL**
- Serum inorganic phosphorus: **5.9 mg/dL**
- Serum intact PTH: **< 3.0 pg/mL**
- Serum thyroid-stimulating hormone (TSH): **2.1 mIU/L** (euthyroid on levothyroxine 100 mcg daily)
- Serum creatinine: **0.9 mg/dL**

Brain CT demonstrated dense, bilateral, confluent calcification throughout the basal ganglia, thalami, centrum semiovale, and cerebellar hemispheres—a radiological hallmark of long-standing hypoparathyroid Fahr syndrome [12,14,15].

Correction of hypocalcaemia was achieved with calcitriol (0.75 mcg daily) and elemental calcium (1,500 mg daily) [1,2]. While neuromuscular irritability and palpitations subsided, her parkinsonian gait, executive dysfunction, and ataxia remained largely unchanged at 12-month follow-up, representing permanent parenchymal damage from chronic mineral dysregulation [8,9,14].

Comparative Summary of Cases

Parameter	Case 1: Osteomalacia	Case 2: Idiopathic Hypoparathyroidism	Case 3: Post-Surgical Hypoparathyroidism
Age / Sex	38 / Female	36 / Male	62 / Female
Primary Mechanism	Impaired gut Ca^{2+} absorption [5]	Autoimmune/idiopathic parathyroid failure [3]	Iatrogenic parathyroid resection/ischemia [1,9]
Serum Calcium	Severely Reduced	Severely Reduced	Severely Reduced
Serum Phosphate	Low/Low-Normal	Elevated	Elevated
Serum intact PTH	High (Secondary Hyperparathyroidism)	Inappropriately Normal/Low	Markedly Suppressed/Undetectable
$\text{Ca} \times \text{P}$ Product	Low	High	High
Primary Complication	Acute Necrotizing Pancreatitis [6,7]	Seizures, Basal Ganglia Calcification [8,13]	Fahr Syndrome (Irreversible Neurodegeneration) [12,14]
Reversibility	Complete clinical resolution	Symptomatic recovery; structural lesions persist [8]	Fixed neurological deficits [9,14]

DISCUSSION

Pathophysiological Dichotomy: Parathyroid Competence Vs. Parathyroid Failure

The biochemical signature of hypocalcaemia depends critically on the functional integrity of the parathyroid gland [1,3]:

- **Secondary Hyperparathyroidism (Case 1):** In severe nutritional osteomalacia, hypocalcaemia triggers robust parathyroid activation. Elevated PTH promotes renal phosphorus wasting, yielding a low-to-normal $\text{Ca} \times \text{P}$ product [4,5]. This biochemical milieu prevents soft-tissue mineralization but accelerates bone demineralization and exposes visceral organs to rapid fluctuations in ionized calcium.
- **Aparathyroidism / Hypoparathyroidism (Cases 2 & 3):** Absence of PTH impairs both bone resorption and distal renal tubular calcium reabsorption while eliminating the primary phosphaturic signal [1,2]. The resulting hyperphosphataemia drives up the circulating $\text{Ca} \times \text{P}$ product, promoting systemic metastatic crystallization across vascular beds and cerebral microvasculature [8,10].

Hypocalcaemia And Pancreatitis: Reverse Causality Vs. Acinar Dysfunction

Hypocalcaemia is typically categorized as a downstream sequela of acute pancreatitis, driven by free fatty acid saponification in peripancreatic fat beds [7]. However, experimental data indicate that profound perturbations in extracellular Ca^{2+} can themselves disrupt the calcium-sensing receptor (CaSR) on pancreatic acinar cells [6,11].

Pathophysiologically, sustained low extracellular calcium triggers abnormal intracellular Ca^{2+} release from the endoplasmic reticulum via inositol 1,4,5-trisphosphate receptors (IP₃R), inducing [6,11,16]:

- Premature intra-acinar activation of trypsinogen to trypsin
- Vacuolization and acinar necrosis
- Dysfunctional ductal secretion and microvascular spasm

While bidirectional causation remains challenging to isolate definitively in humans, patients with severe metabolic bone disease and unexplained abdominal symptoms should be proactively screened for pancreatic enzyme elevation, and vice versa [5,7].

Determinants of Intracranial Calcification and Reversibility

Intracranial mineral deposition in chronic hypoparathyroidism preferentially targets areas of high metabolic rate and microvascular density, including the globus pallidus, caudate

nucleus, and dentate nucleus [8,13]. Hyperphosphataemia induces vascular smooth muscle cells and pericytes to express osteogenic markers, triggering hydroxyapatite precipitation in adventitial layers [8,12,15].

A clear clinical distinction emerges between:

- **Early/Intermediate Phase (Case 2):** Neuromuscular tetany, seizures, and neuropsychiatric disturbances stem predominantly from membrane instability and dynamic neurotransmitter dysfunction; these are substantially reversible upon restoring serum calcium [2,8].
- **Late Phase (Case 3):** Decades of unbuffered mineral precipitation produce neuronal loss, gliosis, and microvascular obliterative sclerosis (Fahr syndrome), resulting in static, irreversible extrapyramidal and cognitive deficits [9,12,14].

Clinical Implications

- **Look Beyond the Value:** Hypocalcaemia must never be managed with empiric oral calcium alone. A minimal initial battery must include simultaneous serum phosphorus, magnesium, alkaline phosphatase, 25-OH vitamin D, and intact PTH [1,4,5].
- **Pancreatic Surveillance in Metabolic Bone Disease:** In patients presenting with acute non-biliary, non-alcoholic pancreatitis, severe vitamin D deficiency and osteomalacia must be ruled out [6,7].
- **Surveillance in Neck Surgery:** Post-thyroidectomy patients require lifelong vigilance. Even in asymptomatic individuals, sporadic surveillance of calcium, phosphorus, and renal function is required to avoid subclinical progression to Fahr syndrome [9,10,14].
- **Target Serum Calcium:** In hypoparathyroidism, therapeutic targets should focus on keeping corrected calcium in the low-normal range (8.0–8.5 mg/dL) while keeping 24-hour urinary calcium < 300 mg/day and the Ca $\times$ P product < 55 mg²/dL² to prevent nephrocalcinosis and cerebral deposition [1,2].

CONCLUSION

Hypocalcaemia spans a broad clinical continuum, ranging from life-threatening abdominal emergencies to progressive neurodegenerative syndromes. Clinicians must recognize that whereas visceral inflammation secondary to osteomalacia may respond fully to

metabolic repletion, delayed recognition of hypoparathyroidism leads to irreversible structural brain calcification [8,14]. A disciplined, etiology-focused approach is essential to arrest disease progression before permanent parenchymal loss occurs.

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