

Familial Hypoparathyroidism

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Abstract

A family with hereditary (familial) hypoparathyroidism is reported where three of the total four siblings were affected and each presented with different manifestation-one brother with refractory epilepsy since early childhood, another brother with unilateral extrapyramidal features in adult life, and their only sister having recurrent attacks of tingling and numbness due to hypocalcemia since 12 years of age.

Introduction

Familial hypoparathyroidism with autosomal dominant inheritance is reported in three siblings.

Case reports

A 21 years old male (AR) presented with rest tremor of right hand for three weeks interfering his daily activities. Examination revealed rigidity, coarse tremor involving all the fingers and wrist of right hand, decreased arm swinging, normal muscle power and normal deep reflexes. Past and personal history was non-contributory.

Routine examination of blood, urine, chest radiography, abdominal ultrasound, and hepatic function tests were normal. Serum urea was 32 mg/dL (normal 15-45 mg/dL) and creatinine 1.1 mg/dL (normal <1.5 mg/dL). Electroencephalogram

(EEG) revealed normal background alpha activity. Computed tomography (CT) scan of brain showed bilateral cerebellar, basal ganglionic, and subcortical calcification (figure 1). A radiological diagnosis of Fahr's disease was made and the patient was further investigated. Total serum calcium was low (6.3 mg %; normal 8.3-10.6 mg %), ionic calcium very low (2.1 mg/dL; normal 4.1-5.6 mg/dL), serum inorganic phosphate elevated (5.6 mg/dL; normal 3-4.5 mg/dL), with raised alkaline phosphatase (596 IU/L, normal 20-130 U/L) and very low serum parathyroid hormone (PTH) level (3.2 pg/mL, normal 10-40 pg/mL). Serum 25 hydroxy vitamin D₃ was 71 ng/mL (normal 15-80 ng/mL) and 1,25 dihydroxy vitamin D₃ 32 pg/mL (normal 25-45 pg/mL). A diagnosis of hypoparathyroidism was made.

Family history revealed that the patient had two elder brothers and one younger sister. His middle brother (HR, aged 24 years) had delayed developmental milestones and recurrent attacks of convulsion since two years of age. At present he is on phenytoin, valproate and clobazam regularly with seizures

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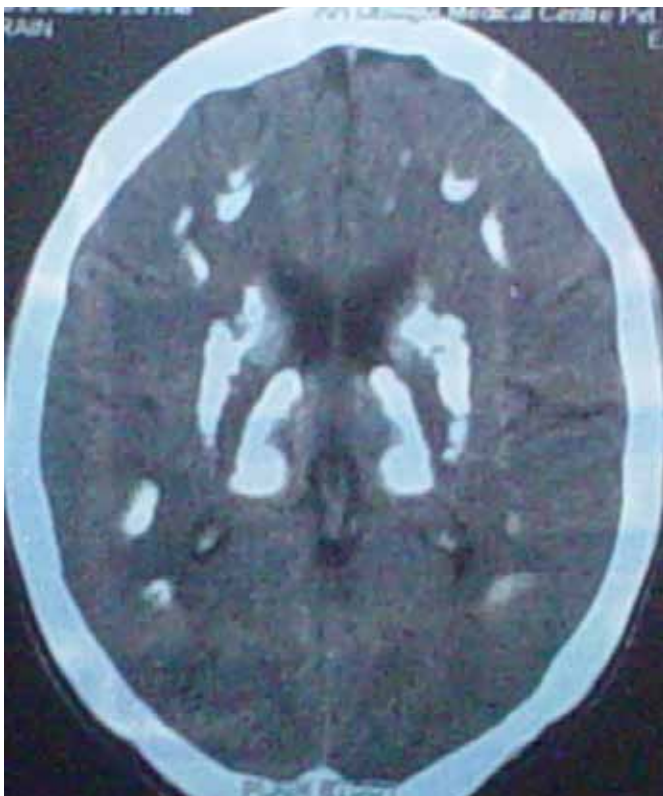


Fig. 1 : CT scan of Brain of the proband showing bilateral basal ganglia and subcortical calcification.



Fig. 2 : CT scan of brain of the middle brother showing gyral, subcortical and basal ganglia calcification.

still uncontrolled. He had no neurodeficit and Weschlers' adult intelligent scale diagnosed moderate mental retardation with a score of 46. Resting EEG showed bilateral, paroxysmal, symmetrical high amplitude slow waves on an alpha background suggestive of interictal pattern and CT scan of brain was almost identical to that observed in the proband (figure 2). Serum creatinine was 1.1 mg/dL. Biochemical investigations were also suggestive of hypoparathyroidism state (ionic calcium 2.5 mg/dL, inorganic phosphate 5.2 mg/dL, alkaline phosphatase 630 U/L, and parathyroid hormone 2.9 pg/mL).

The proband's younger sister (SP, aged 17 years) had recurrent attacks of tingling and numbness, usually precipitated by anxiety and stress, involving the distal extremities since her 12 years of age with out any motor deficit, sphincteric disturbances, convulsion, abnormal movements or loss of consciousness. Each episode used to resolve spontaneously. Her problem was never investigated or treated. She also had similar biochemical abnormalities (ionic calcium= 1.1 mg/dL, inorganic phosphate= 5.8 mg/dL, parathyroid hormone= 8.9 pg/mL) suggestive of hypoparathyroidism. Her cranial CT scan, EEG, and other routine investigations were normal with a serum creatinine of 0.8 mg/dL.

A clinical diagnosis of familial/idiopathic hypoparathyroidism was made. Search for deficiencies of other endocrine organs yielded negative results. Evaluation of their parents (non-consanguineous) and the eldest brother (MR, aged 26 years) did not reveal any clinical, biochemical or EEG/CT abnormality. All relevant investigations in proband's two maternal uncles and two (paternal) cousin brothers were also normal.

Discussion

Familial hypoparathyroidism is a genetically heterogeneous group of disorders that may be isolated, or be associated with congenital or acquired abnormalities in other glands or developmental anomalies.^{1,2} X-linked recessive, autosomal dominant and autosomal recessive- all types of inheritance has been reported. The disease often manifests in the first decade, but may appear later. Participation of PTH receptor 2 in the brain and superoxide production by mitochondria leads to intracerebral calcification.³

Bilateral calcification in the basal ganglia associated with neurological manifestations is classically diagnosed as Fahr's disease.⁴ Several metabolic derangements have been associated with this entity, particularly parathyroid disorders (idiopathic hypoparathyroidism, psuedohypoparathyroidism or secondary hypoparathyroidism of renal disease).⁴ Other causes include congenital toxoplasmosis, mitochondrial cytopathies, idiopathic cerebrovascular ferrocalcinosis, Cockayne syndrome, carbon monoxide or lead poisoning, and rarely Wilson's disease.⁴ Movement disorders are found in 55%, of which Parkinsonism accounts for 57%, chorea 19%, tremor 8%, dystonia 8%, athetosis 5%, and orofacial dyskinesia 3%.⁴ Other manifestations include seizures, cognitive impairment, cerebellar signs, dysphasia, pyramidal signs, psychiatric features, gait disorders, and sensory changes depending on extent of calcification.^{4,5}

Gain-of-function mutations in the calcium-sensing receptor cause autosomal dominant hypocalcemia.⁶ The activated receptor suppresses PTH secretion, leading to hypocalcemia; receptor activation in the kidney results in excessive renal calcium excretion.⁶ Recognition of this syndrome is important because efforts to treat the hypocalcemia in these patients with vitamin D analogues and increased oral calcium exacerbate the already excessive urinary calcium excretion, leading to

irreversible renal damage from stones and ectopic calcification.⁶

The proband had two elder brothers and one younger sister. The eldest brother was unaffected, the middle brother and sister were both affected. The disease showed complete penetrance with variable expressivity indicating the possibility of dominant inheritance of a mutation that probably occurred in any of the parents. It is interesting to note that each of them had different presentation- one presented with epilepsy since childhood, another with unilateral extrapyramidal symptoms manifesting first in adult life, and their only sister developed neuromuscular irritability of hypocalcemia in her peripubertal life. All of them were treated with vitamin D₃ and oral calcium. Symptoms subsided in the younger brother (AR) and sister though the middle brother (HR) continued to get attacks of seizures.

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