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Short communication

Idiopathic Hypoparathyroidism: New Insights into an Enigma

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Abstract

Calcium is a very important electrolyte - necessary for neurotransmission, cell signaling, and bone development. Hence, blood calcium levels are to be kept in a safe normal range. The parathyroid hormone has an important role in calcium metabolism at the level of the bone, kidney, or GI tract. Hypoparathyroidism is a condition of reduced formation of parathyroid hormone.

Key words: hypocalcemia; hyperphosphatemia; hypoparathyroidism; idiopathic; GCM2

Introduction

Calcium is a very important electrolyte - necessary for neurotransmission, cell signaling, and bone development. Hence, blood calcium levels are to be kept in a safe normal range. The parathyroid hormone has an important role in calcium metabolism at the level of the bone, kidney, or GI tract [1]. Hypoparathyroidism is a condition of reduced formation of parathyroid hormone. It may lead to hypocalcemia, low calcitriol, and hyperphosphatemia.

Idiopathic hypoparathyroidism (IHP) is an uncommon endocrine disease, with highly variable clinical manifestations. Its incidence ranges from 0.55 to 0.88/100,000 in Asian populations [2]. It can occur as an isolated disease or as part of many syndromes. The etiology is labelled as idiopathic if no cause is found after excluding all possible etiologies. Idiopathic hypoparathyroidism may have a hidden genetic etiology [3]. Molecular genetic analyses over the past few decades have recognized mutations in many genes which have given us new insights into embryological development of the parathyroid glands, regulation of parathyroid hormone (PTH) synthesis and secretion, and maintenance of parathyroid gland homeostasis [4]. The quality of life (QoL) is affected in patients causing a reduced sense of well-being. But there is no conclusive evidence regarding increased mortality in patients having hypoparathyroidism [5].

Due to highly nonspecific and varied manifestations, idiopathic hypoparathyroidism often has a long lag period of diagnosis and increased

risk of misdiagnosis. A serum calcium profile in patients with trivial issues like paresthesia may avoid the lengthy delay as well as misdiagnosis of patients having idiopathic hypoparathyroidism [6].

Autoantibodies against cytoplasmic parathyroid tissue may be found in up to 30–70% of patients having IHP. Treatment target is to restore calcium levels. To prevent hypocalcaemia, patients of hypoparathyroidism require lifelong calcium supplementations and calcitriol to stimulate absorption of calcium and phosphate in the gut. A diet containing high-calcium and low phosphorus is recommended.

In a previous report of two cases, we have established the critical role of GCM2 activity in human parathyroid gland development through clinical and genetic analysis of 2 patients with hypoparathyroidism. These conclusions have more immediate relevance for the diagnosis and treatment of cases having isolated hypoparathyroidism [7].

At our institution we have experience of a small but significant number of patients with IHP. Similar reports have been available from other Endocrine departments as well. Hence, with the availability of diagnostic tools like NGS being more common place, we can arrive at a definitive genetic diagnosis; proving useful in prognosticating the disease severity & requirement of therapy. In inherited cases genetic counseling of patients can also be done.

Genetic Disorders Associated with Hypoparathyroidism

Disease	Inheritance	Gene	Locus	Prevalence	Comorbidities				
A. Disorders of parathyroid gland formation									
Isolated parathyroid	AR or ADXR	GCM2	6p23-						
aplasia		SOX3	24Xq26–27						
DiGeorge Syndrome	Sporadic or AD	TBX1	22q11.21-	1:4,000-	Thymic hypoplasia with immune				
type 1	a 1: 15		q11.2310p13	1:7,692	deficiency, conotruncal cardiac				
DiGeorge Syndrome	Sporadic or AD	NEBL			defects, cleft palate, dysmorphic facies				
type 2									
Charge Syndrome	Sporadic or AD	CHD7	8q12.27q21.1	1:8,500	Cardiac anomalies, cleft palate,				
		SEMA3E	1		renal anomalies, ear abnormalities/				
					Deafness and developmental delay				
Hypoparathyroi-dism,	AD	GATA3	10p14–15		Deafness and renal dysplasia				
deafness, and renal									
dysplasia Hypoparathyroidism,	AR	TBCE	1q42-43		Growth retardation, developmental				
retardation and	AK	IBCE	1442-43		delay, dysmorphic facies				
dysmorphism					detay, dysmorphic facies				
Kenny-Caffey	AR	TBCE	1q42-	1:40,000 -	Short stature, medullary stenosis,				
syndrome type 1			4311q12.1	1:100,000 in	dysmorphic facies, developmental				
			_	Saudi Arabia	delay				
					Similar to type 1, but clinically				
Kenny-Caffey					distinguished by the absence of				
syndrome type 2	AD	FAM111A			mental retardation				
Mitochondrial disease	Maternal	Mt DNA			Encephalomyopathy,				
Kearns-Sayre					ophthalmoplegia, retinitis pigmentosa and heart block				
syndrome Pearson Marrow		Mt DNA			Pancreatic dysfunction, sideroblastic				
Pancreas syndrome		WILDINA			anemia, neutropenia, and				
Tancreas syndrome					thrombocytopenia				
MELAS		Mt tRNA			Mitochondrial myopathy,				
					encephalopathy, lactic acidosis, and				
					stroke-like episodes				
LCAHD		MTP	2p23.3		Impaired vision, night blindness,				
					rhabdomyolysis, cardiomyopathy				

B. Disorders of parathyroid gland formation

MCADD		ACADM	1p31.1	1:17,000	Fasting hypoglycemia,			
C. Disorders of parathyroid hormone synthesis or secretion								
PTH gene mutations	AD or AR	РТН	11p15.3- p15.1					
AD hypocalcemia type 1	AD or sporadic	CASR	3q13.3- q21.1		Hypercalciuria			
AD hypocalcemia type 2	AD or sporadic	GNA11	19p13.3					
D. Disorders of parathyroid gland destruction								
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	AR, AD or sporadic	AIRE	21q22.3	1:90,000 – 1:200,000	Mucocutaneous candidiasis, Adrenal insufficiency, and Primary hypoparathyroidism			

Abbreviations

IHP- Idiopathic Hypoparathyroidism

GI- Gastrointestinal

PTH- Parathyroid Hormone

QOL- Quality of Life

NGS- Next Generation Sequencing

GCM2- Glial cell missing homolog 2

Mt DNA- Mitochondrial DNA

MELAS- Mitochondrial Encephalomyopathy, Lactic acidosis, Stroke-like Episodes

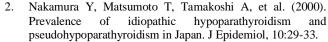
ACADM- Acyl CoA dehydrogenase medium chain

LCAHD- Long Chain Hydroxy-acyl CoA Dehydrogenase

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