

### **Neonatal Hyperparathyroidism: Adenoma or Mutation?**

We read with interest the letter by Shah and Shah published in November 2003 issue of the Journal(1). The authors report a neonate with symptomatic hypercalcemia, high blood levels of parathormone (PTH) and normal urinary calcium excretion. Radiological evaluation showed a parathyroid mass, which was excised with satisfactory results. Their conclusion that the cause of hypercalcemia was a parathyroid adenoma however needs reconsideration.

We recently saw a similar neonate who presented with hypercalcemia at 15 days of life. This boy, born of a non-consanguineous marriage, presented with lethargy, poor feeding, persistent vomiting and dehydration. Investigations revealed serum calcium levels varying between 15-18 mg/dL and phosphorus 4-4.5 mg/dL. His serum PTH levels were 75 pg/L (normal values 10-60 pg/L) and urinary calcium excretion was low (ratio of spot urine calcium to creatinine 0.2; normal for this age 0.6). CT examination of the head showed abnormal calcifications in the basal ganglia and frontal cortex. Ultrasound examination of the abdomen showed bilateral medullary nephrocalcinosis. A diagnosis of neonatal severe hyperparathyroidism (NSHPT) was made. Following localization of the glands on parathyroid scintigraphy, the glands were totally excised; one-half gland was placed subcutaneously in the right infrascapular region. Biopsy of excised parathyroid glands was suggestive of chief cell hyperplasia. Both parents had normal levels of blood calcium; urinary

calcium excretion was reduced ( $U_p/U_c = 0.05$  and 0.08).

Primary hyperparathyroidism is a rare condition in the neonatal period. However there is increasing realization that hyperparathyroidism at this age is chiefly the result of a defect in calcium homeostasis mediated by the calcium sensing receptor (CaR).

CaR is plasma membrane G-protein coupled receptor expressed primarily on the PTH producing chief cells of the parathyroid gland, proximal renal tubular cells, bones and intestines(2). They are highly sensitive to small changes in the extracellular concentrations of calcium, and therefore key mediators of calcium homeostasis. Low serum calcium evokes a CaR mediated increase in PTH production resulting in mobilization of calcium from the bones to the extracellular fluid. Similarly, a high calcium concentration suppresses the activity of CaR. The genetic locus for the receptors has been mapped to the short arm of chromosome 3(3).

Abnormality of these receptors leads to dysregulation of calcium homeostasis. An inactivating mutation of the locus results in a higher set point of the parathyroid gland receptors for sensing plasma calcium resulting in hypercalcemia with very low urinary excretion of calcium (hypocalciuric hypercalcemia). On the other hand, an activating mutation results in hypocalcemia with hypercalciuria.

The phenotype of inactivating mutation is variable but usually corresponds to the genotype. Thus heterozygous inactivating mutations result in the syndrome of familial hypocalciuric hypercalcemia, which is usually asymptomatic(4). Homozygous mutations or

a compound heterozygous state result in moderate to severe hypercalcemia in the neonatal period labeled as NSHPT. Most neonates with NSHPT require subtotal or complete parathyroidectomy.

In view of presentation in the neonatal period, symptomatic hypercalcemia and low to normal urinary calcium excretion, we believe that an inactivating mutation of the CaR was responsible in both the above patients. A primary adenoma of the parathyroid gland, as proposed by Shah and Shah(1), would on the other hand, be associated with increased urinary calcium excretion (proportionate to the degree of hypercalcemia). Careful assessment of urinary calcium excretion (on one or more occasions) is thus useful in differentiating a primary adenoma of the parathyroid gland from an inactivating receptor mutation. Estimation of blood and urinary levels of calcium in parents and siblings may also provide important information.

We emphasize that most cases of primary hyperparathyroidism in neonates and infants are due to a defect in CaR receptor rather than a primary adenoma(5). An extensive radiological evaluation of parathyroid glands is rarely necessary. The management strategy in

such patients chiefly depends on the severity of the metabolic abnormalities.

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### **A Rare Cause of Congestive Heart Failure in Newborn**

Arteriovenous malformations (AVMs) are rarely seen in neonates and most often present with congestive heart failure (CHF). We report a newborn with congestive heart failure due to AVM in the posterior fossa.

A term male baby was admitted to neonatology department with respiratory distress at 5 hour of life. On physical examination perioral cyanosis, dyspnea, tachypnea and a grade 3/6 systolic ejection murmur at left lower sternal border were noticed. These factors lead to the diagnosis of CHF. On echocardiography only right atrial, ventricular and superior vena cava