The Turkish Journal of Pediatrics 1999; 41: 253-257 *Case*

CONGENITAL PRIMARY HYPOPARATHYROIDISM PRESENTED WITH EXTENSIVE CUTANEOUS AND SUBCUTANEOUS CALCIFICATIONS*

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SUMMARY: Aslan Y, Gedik Y, Ökten A, Aksoy A, Çimşit G, Ari N. (Departments of Pediatrics, Dermatology and Pathology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Congenital primary hypoparathyroidism presented with extensive cutaneous and subcutaneous calcifications. Turk J Pediatr 1999; 41: 253-257.

Congenital primary hypoparathyroidism is very rare in infancy. It may be isolated or associated with other developmental defects, arising from the third and fourth pharyngeal pouches such as DiGeorge syndrome. Initial symptom of isolated primary hypoparathyroidism in an infant is usually generalized convulsion due to hypocalcemia. However, the clinical spectrum of DiGeorge's anomaly is highly variable. We report a two-hour-old neonate with congenital hypoparathyroidism presenting with extensive cutaneous and subcutaneous calcifications. To our knowledge, extensive calcification of the skin and subcutaneous tissue as a presenting feature of congenital primary hypoparathyroidism in an infant is reported for the first time. *Key words: congenital hypoparathyroidism, extensive calcifications.*

Hypoparathyroidism results from failure of parathyroid hormone (PTH) synthesis or secretion (true or primary hypoparathyroidism) or from resistance to the actions of PTH (pseudohypoparathyroidism)[1,2]. Hypoparathyroidism is very rare in infancy, but is an important disease in childhood[3]. The majority of cases with congenital hypoparathyroidism ar a component of DiGeorge's anomaly resulting from the defective development of third and fourth pharyngeal pouches; only a minority of the cases have isolated disease[2]. Isolated congenital hypoparathyroidism usually presents as a generalized neonatal convulsion due to hypocalcemia that relapses at each attempt to stop the treatment beyond six months of age. However, the clinical spectrum of DiGeorge's anomaly is highly variable[2].

Calcification is the result of deposition of calcium and phosphate in organic matrices of the tissue[4]. Cutaneous calcification may be divided into four categories: dystrophic, metastatic, idiopathic and iatrogenic. Metastatic calcification results from abnormal calcium and/or phosphate metabolism and occurs in a wide variety of unrelated diseases[4,5].

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This report describes a newborn baby with congenital hypoparathyroidism presented with extensive cutaneous and subcutaneous calcifications. As far as we know, extensive calcification of cutaneous and subcutaneous tissues as a presenting feature of congenital primary hypoparathyroidism in an infant has not previously been reported.

Case Report

A two-hour-old female infant was referred to our neonatal intensive care unit for evaluation of multiple cutaneous tumors. She was the fifth child of unrelated and healthy parents, and was born following a full-term uncomplicated gestation. Parental history revealed that two male siblings of the patient had died due to diseases presented with hypocalcemic convulsion during the early neonatal period. One female sibling had DiGeorge syndrome due to encephalitis at 11 years of age.

Physical examination revealed weight 3,950 g, length 51 cm, respiratory rate 42 breaths/min, heart rate 176 beats/min, blood pressure 78/46 mmHg, and temperature 36.8 °C. Her general condition was good. Deep tendon reflexes were brisk. Multiple hard and milky subcutaneous nodules were noticed on each side of the body. These nodules quickly became larger and many new nodules became visible. Tremors and convulsions lasting a few seconds to a few minutes developed, and Chvostek's sign was elicited during the second hour of admission. All other findings on physical examination were normal. On enquiry, the obstetrician reported the presence of metastatic calcifications on the placenta and umbilical cord.

Laboratory investigations included a leukocyte count of 8,200/μl, hemoglobin 14 g/dl, hematocrit 43.6 percent, platelet count 362,000/μl, glucose 78 mg/dl (normal 30 to 91), total calcium (tCa) 4.3 mg/dl (normal 7.3 to 9.2), ionized calcium (iCa) 1.8 mg/dl (normal 4.48 to 4.92), phosphorus (P) 12.1 mg/dl (normal 2.9 to 8.1), alkaline phosphatase 216 U/L (normal 150 to 400), total protein 6.2 g/dl (normal 5.8 to 8.2), albumin 3.1 g/dl (normal 3.3 to 4.5), magnesium 2.36 mg/dl (normal 1.20 to 2.50), C-terminal specific PTH 4.1 pmol/L (normal 22 to 66), 25 (OH) vitamin D 28 ng/ml (normal 20 to 60), and normal urea, creatinine, uric acid, electrolyte values and liver function tests. Urinalysis and initial arterial blood gases were within normal limits. The electroencephalogram showed a paroxysmal dysrhythmia, and electrocardiogram revealed marked lengthening of the QT segment and superimposition of T on P wave. Chest x-ray showed normal thymic shadow, and limb x-rays demonstrated multiple calcifications (Fig. 1). Ultrasonographies of the thymus, abdomen and cranium demonstrated normal findings. Results of studies for sepsis were negative and chromosomal analysis was normal. Immunological investigations revealed a lymphocyte count 3,444/μl (normal 2,000 to 11,000), T lymphocyte (CD3+ cell) percentage 73 (normal 60 to 75), CD3+ cell count 2,445/μl (normal 1,300 to 4,000), and CD4+ cell/CD8+ cell ratio 1.74 (normal 1.5 ± 2.2).

A skin biopsy adjacent to the nodular lesions was performed and submitted for histopathological study. Hematoxylin and eosin-stained sections of the skin biopsy material revealed numerous calcified deposits (Fig. 2a, b).

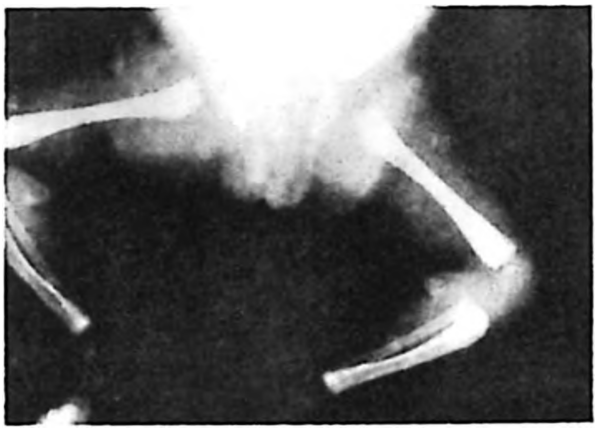
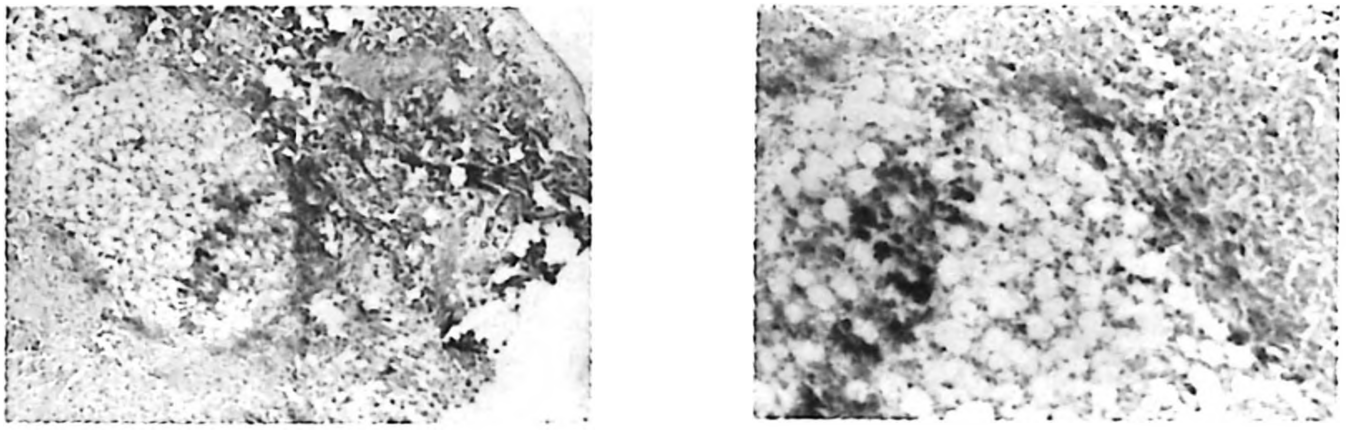


Fig. 1: X-ray film of the lower extremities showing multiple subcutaneous calcifications.



(a) (b)

Fig. 2a, b: Hematoxylin- [(a) H.E. x 40] and eosin-stained [(b) H.E. x 200] section of the skin biopsy showing numerous calcified deposits.

A diagnosis of idiopathic congenital hypoparathyroidism was made. She was given intravenous calcium gluconate (75 mg elemental Ca/kg/day), intravenous diazepam (0.5 mg/kg), 1,25 dihydroxyvitamin D (0.5 µg/kg/day), and aluminum hydroxide (100 mg/kg/day). Clinical and electrical seizures persisted; therefore, intravenous phenobarbital (20 mg/kg) and subsequently intravenous phenytoin (15 mg/kg) were added.

At the age of 24 hours, laboratory studies demonstrated tCa 5.1 mg/dl (normal 6.9 to 9.4), iCa 2.3 mg/dl, P 10.9 mg/dl (normal 2.9 to 8.1), total protein 6.5 g/dl (normal 5.8 to 8.2), albumin 3.4 g/dl, PTH 5.7 pmol/L, and magnesium 2.91 mg/dl. Electrolyte values were normal, and arterial blood gases demonstrated

mild hypoxemia. At the age of 45 hours, the patient, whose seizures repeated intermittently, developed ventricular arrhythmia secondary to hypocalcemia and died due to cardiorespiratory arrests that developed suddenly.

In order to determine a cause for the infant's hypocalcemia, the mother, father and sister of the patient were examined in our hospital. Their physical and laboratory findings, including Ca, P, and PTH levels, and chromosomal analyses were normal.

Discussion

Calcium is vital to many biologic processes. Serum Ca is tightly regulated by PTH and 1,25 dihydroxyvitamin D. Despite this careful regulation, calcification and ossification of cutaneous and subcutaneous tissues may occur[5]. Metastatic calcification occurs in diseases with chronically elevated serum Ca or P levels such as hyperparathyroidism, hypervitaminosis D, milk-alkali syndrome, chronic renal disease, sarcoidosis, pseudoxanthoma elasticum, destructive bone disease with excessive osteoclastic activity and others. All tissues may be affected, but skin involvement is rare[6].

Subcutaneous calcification and/or ossification may be the persisting feature of both pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism exhibiting characteristic phenotypic abnormalities[7]. Aberrant calcifications may also occur in patients with hypoparathyroidism, but they are usually intracranial, most often in the basal ganglia. Furthermore, these are usually seen in patients with acquired hypoparathyroidism resulting from alteration or injury to the parathyroid glands in the course of thyroid or other neck surgery[8]. Goldminz et al.[9] reported an adult patient with hypoparathyroidism who developed dermal calcification along the path of an infiltrated calcium chloride intravenous infusion.

Although the etiology remains obscure, X-linked recessive, autosomal dominant and autosomal recessive familial types of isolated primary hypoparathyroidism have been reported[1, 10]. Autosomal dominant form of congenital hypoparathyroidism with onset during the neonatal period is usually symptomatic, but some reports have noted the rare occurrence of autosomal dominant hypoparahyroidism with a benign course[1]. However, there is no known feature of DiGeorge syndrome that uniformly occurs[11]. The disorder is usually sporadic, but autosomal dominant and autosomal recessive inheritance have been reported[2, 11]. The most complete form includes aplasia of the parathyroid glands with complete hypoparathyroidism, thymus aplasia with severe T-cell immunodeficiency, cardiovascular malformations, and particular facial dysmorphies. In such cases, early diagnosis is mainly based on the association of hypocalcemia and the absence of the thymus on chest x-ray. However, there are milder forms of hypoparathyroidism with thymus hypoplasia without immunodeficiency or other features[2].

In the present case, there was no documented feature of DiGeorge's anomaly other than hypoparathyroidism. However, parental history revealed the presence of one sibling with DiGeorge's anomaly. Due to the lack of detailed genetical investigations and postmortem examination of the thymus, a diagnosis of isolated hypoparathyroidism or partial DiGeorge's anomaly could not be confirmed.

The initial symptom of hypoparathyroidism in the infantile period is usually generalized convulsion due to hypocalcemia[3]. In the peresent case, congenital hypoparathyroidism presented with excessive cutaneous and subcutaneous calcification at delivery.

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