SEVERE FORM OF INFANTILE IDIOPATHIC HYPERCALCEMIA
Report of a Case

Mithat Çoruh, M.D.*, and Gönül Argun, M.D.**

Idiopathic hypercalcemia was first described by Butler [1] and Fanconi [2] almost simultaneously in 1951. Both of the infants described showed growth retardation plus anorexia and osteosclerotic changes in the bones. Their serum calcium levels were also high. The case reported below is of a severe form of idiopathic hypercalcemia and is, we believe, the first case to be reported in Turkey.

Case Report

N. T., a 14 month old girl, was born after an uncomplicated pregnancy and delivery. Her birth weight was 3,900 Gm. She was well until four months of age when she became anorexic and began to have frequent infections and fevers. She was not yet sitting up when we saw her at 14 months of age. Her first teeth had erupted at five and one-half months, and she had been given vitamin D supplements (100,000 u. daily) after the age of four months. The patient had one sister, six years old, in apparent good health. The father, a physician, and the mother were both healthy. The patient was five months old when first seen at Hacettepe Children's Hospital. Her complaints at that time included anorexia, vomiting, constipation, diarrhea, and frequent temperature elevations.

Physical examination (on first admission): Head circumference: 41 cm.; weight: 6,280 Gm; height: 61 cm. Examinations of other systems were found to be within normal limits. No comment was made about her facial appearance.

Laboratory examination: Hb: 10, 850 gr per 100 ml; WBC: 6, 600 per mm with a normal differential. Many leucocytes and leucocyte clumps were visible in the urine under hpf microscope. E. coli was cultured from the urine and was resistant to all antibiotics and sulphonamides. NPN was 53.5 mg per cent, and an intravenous pyelogram was reported to be normal. Various types of antibiotics were used including Kanamycin and Furadantin (nitrofurantoin), to clear the urinary infection, without any benefit. The patient was discharged with a diagnosis of urinary tract infection.

The patient was re-hospitalized at the age of 14 months with the same complaints, plus growth retardation. Her parents reported that she showed evidence of a peripheral type of facial palsy and conjunctivitis two months prior to the second admission. She had been given two shots of vitamin D (600,000 units each) because of anorexia and hypotonia 15 days apart, the second shot being given one month prior to the second admission.

From Ankara University Hacettepe Medical Center and Hacettepe Children's Hospital.
* Adolescent specialist
** Pediatrician

Physical examination (second admission): Temperature: 37.7 C; pulse: 130 per minute; blood pressure: 140/85 mm; weight: 7.0 kg; height: 72 cm. In general she appeared to be alert, although pale and unhappy. She was significantly hypotonic. Head circumference was small for her age (42 cm), and she was generally physically retarded. Her facial appearance was typical of idiopathic infantile hypercalcemia (Figure 1) with wide

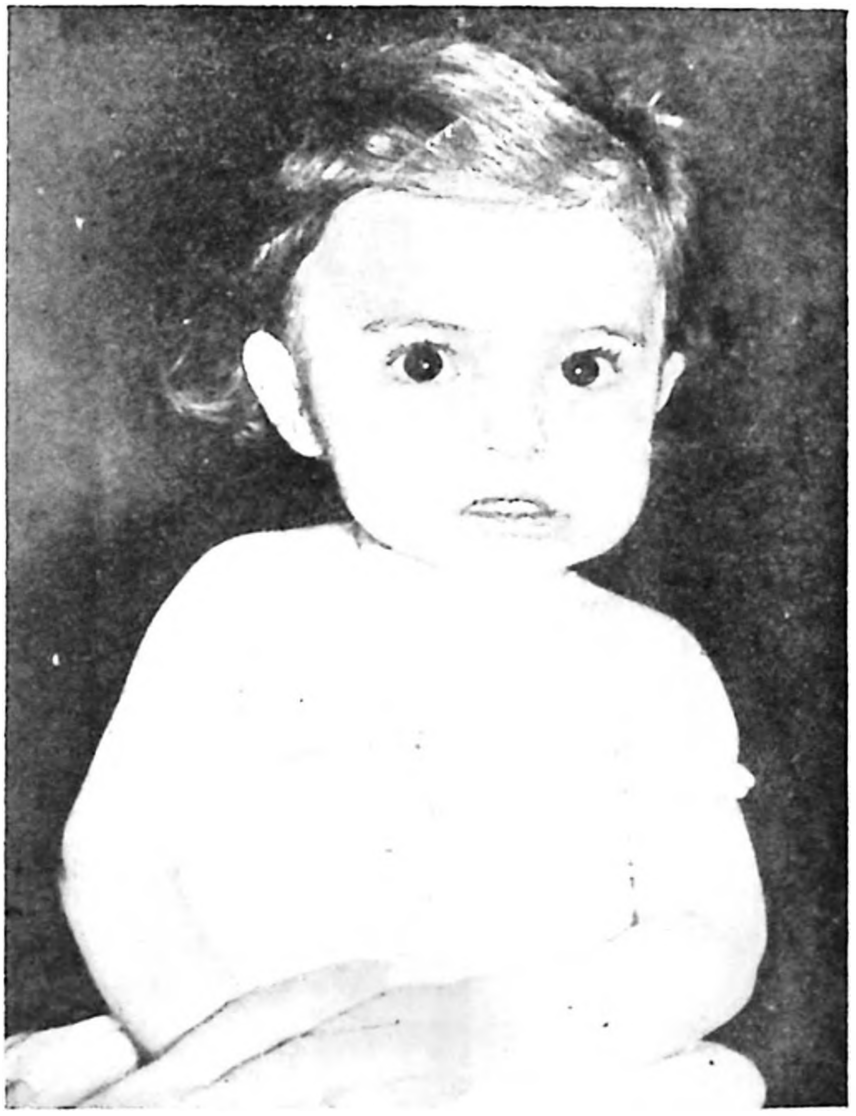

Figure 1. Shows typical facial appearance of patients with idiopathic infantile hypercalcemia.

forehead, large eyes with slight hypertelorism, depressed nasal bridge, and prominent and low-set ears. The mandibula was hypoplastic. Her mouth was big but the upper lip was not overhanging. Tachycardia was evident but no murmur was heard over the precordium. Blood pressure was consistently high (140/85 to 160/90 mm). Lungs were clear on percussion and auscultation. There was no palpable organ or mass in the abdomen. Deep tendon reflexes were somewhat depressed, although no pathological reflexes were elicited. She recognized her father and mother, and reacted to strangers. She was able to sit by herself for short periods of time, and was able to use her hands precisely. She immediately brought up to her ear any object placed in her hands.

Laboratory examination: Hb: 11.55 gm per 100 ml; WBC: 8,600 cu mm; urine: acid; protide: negative; Sulkowitch test: 1 to 2 plus; sugar and acetone: negative; specific gravity: 1.010; urine sediment: 8 to 10 white cells (hpf) and occasional leucocyte clumps; u ine culture: E. coli; serum Ca: 16.5 mg per cent; P: 5.2 mg per cent; alkalin phosphatase: 5. 3 B. U.; NPN: 51 mg per cent. Serum proteins: total protein: 7.1 Gm per cent; albumin: 5.3 Gm per cent; globulin: 1.8 Gm per cent; Co2: 16.38 mEq per liter; Cl: 108.5 mEq per liter; Na: 130.0 mEq per liter; K: 4.5 mEq per liter; PPD (five units): negative. Serum vitamin A level: 68 micrograms per cent (227 i. u.); serum carotin: 2.8 mg per cent; cholesterol: 214 mg per cent. Kreatinin and inulin clearance test results were both very low (kreatinin: 21.8 per minute; inulin: 8.42 cc per minute).

Electrocardiogram showed sinusal tachycardia.

X-ray examination: IVP and x-rays of the extremities were reported to be within normal limits. An x-ray of the skull revealed osteosclerotic changes, especially at the base of the skull (Figure 2, a and b).

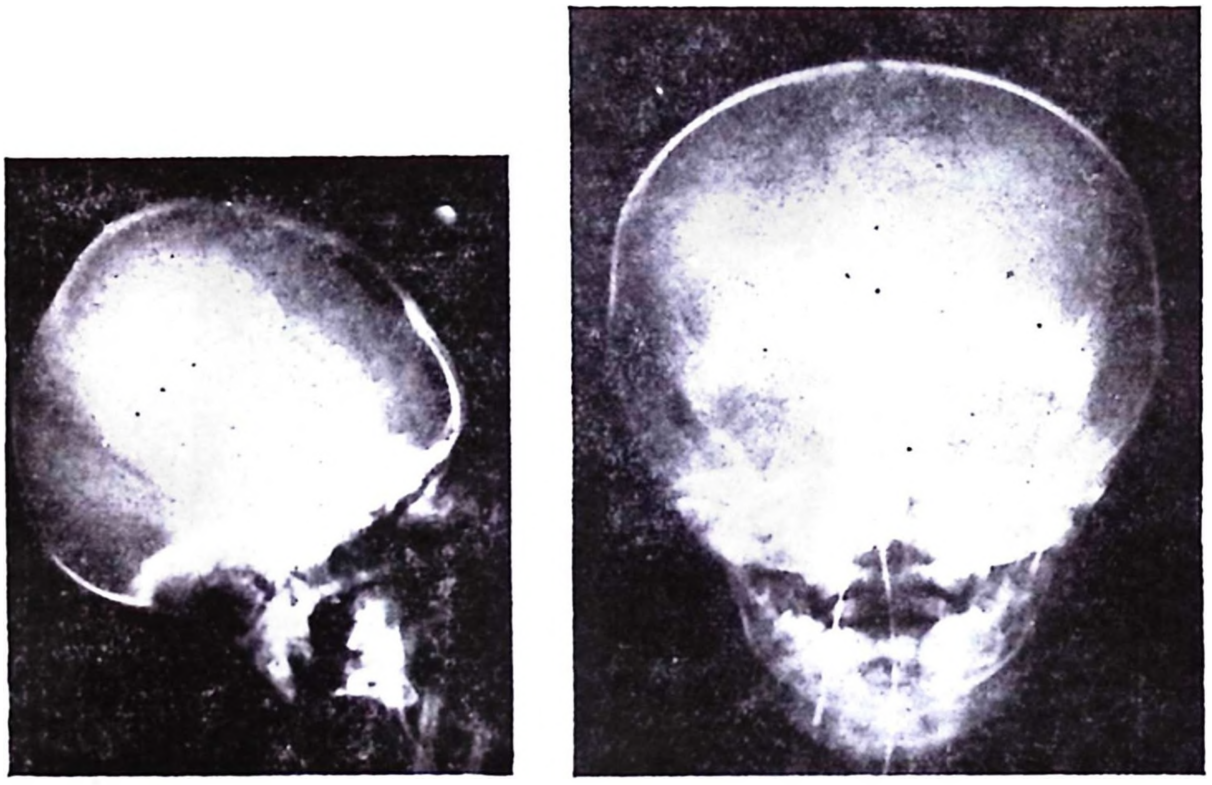

Figure 2 a and b. Osteosclerotic changes of the skull in idiopathic infantile hypercalcemia.

The patient was placed on a low calcium diet and was given initially 20 mg of prednisilone daily. Serum Ca dropped to 11.2 mg per cent after two weeks and the patient began to gain weight. After a month of treatment, x-rays revealed no evidence of osteosclerotic changes of the skull. The patient was discharged from the hospital, but continued on 5.0 mg prednisilone per day, and her parents were instructed to give her a low calcium and vitamin D diet.

Discussion

One common observation in cases of infantile idiopathic hypercalcemia is failure to thrive. Most of the patients have anorexia and vomiting. Two forms of the disease have been recognized. The benign form, which is self-limiting, is usually caused by sensitivity to an overdose of vitamin D (over 1500 i. u. daily). Patients with this form of the disease have anorexia, vomiting and constipation. The severe form may occur in these infants even if they do not recieve an overdose of vitamin D. Cases have been reported dealing with patients as young as two months, who had symptoms of hypercalcemia. [3]

Another common characteristic of the disease is the similarity of facial appearance of the patients, as if they were all from the same family. This typical appearance is called "elfin face", and is characterized by a high and wide forehead, large eyes with epicanthal folds, convergent strabismus, and hypertelorism. The mouth is generally large with the upper lip overhanging, and the ears prominent and low–set. It is reported, however, that some patients do not have this typical elfin face. Mental retardation and poor kidney function have been reported frequently but it is not clear whether this is due to the toxic effect of high serum calcium on the body tissues or to a congenital defect.

These patients are almost always hypotonic in contrast to their alert look. Serum calcium levels are usually over 11.5 mg per cent and this fact is essential to the diagnosis of the condition. [4,5] Serum alkalin phosphatase and phosphorus are usually within normal limits, although serum phosphorus levels may be high if there has been severe kidney damage. Fellers, et al, found moderately low levels of alkalin reserve. These investigators also reported that serum vitamin A and carotin levels are higher than normal. Serum sodium, potasium and chlorides are usually within normal limits, but serum cholesterol may be high.

X–rays are helpful in diagnosis of the disease. Those of the skull usually reveal osteosclerotic changes and long bone surveys may show increased density at the ends of these bones. [7] Severe cases of idiopathic hypercalcemia have been reported in which there were no osteosclerotic changes, and in at least one case there was evidence of demineralization of the bones. [5]

Intravenous pyelograms are usually normal except that they may show poor renal concentration of the injected dye.

The fontanel may close prematurely and early synostosis of the sutures may be complicated by craniostenosis. Asymptomatic heart murmurs

have been reported in the literature. At autopsy, some myocardial changes have been noted which have probably been caused by high calcium levels. Some authors, however, have reported congenital supravalvular stenosis apparently not due to the hypercalcemia.

Recently a new syndrome was described with mental retardation and supravalvular aortic stenosis.[8,9,10] These patients all had the facial appearance characteristic of idiopathic hypercalcemia. Since we do not know anything about their serum calcium levels in infancy, it would be hard to say that the patients developed these symptoms as a result of hypercalcemia.

The etiology of the disease is unknown. Sinclair[11] hypothesized that a deficiency of essential fatty acids in cow's milk is probably the cause. James and Stapleton[12] however showed in their balance study that essential fatty acids did not decrease the serum calcium level permanently. Fanconi[2] thought that this syndrome is a collection of several congenital defects. Bongiovanni believed that congenitally immature tubules of the kidneys did not respond properly to parathormone and thus caused an elevation in serum calcium levels.[4] Fellers[13] believes that there is a defect in vitamin D metabolism. He noted serum vitamin D levels are consistently high in these patients, even though they were not given excessive amounts.

There is little difficulty in making a differential diagnosis in typical cases. Vitamin D intoxication can be differentiated by the history and the benificial effects of decreased vitamin D intake. Low phosphorus and high alkalin phosphatase levels distinguish hyperparathyroidism from hypercalcemia. X-rays may show cystic formations in the bones of patients with hyperparathyroidism, in contrast to the idiopathic hypercalcemic patients who generally show increased bone density. In renal acidosis serum calcium may be elevated, but these patients also have hyperchloremic acidosis and alkaline urine. In addition, hypotonia is not characteristic of hyperchloremic acidosis.

Prognosis and Treatment

Early diagnosis and treatment effect the prognosis of the disease. The reported cases of severe idiopathic hypercalcemia are not an adequate basis for forming generalizations about the prognosis of the disease, but the impression is that the prognosis is good if the patient receives proper treatment before the age of one or two years. Treatment should be continued at least for two to three years. The prognosis depends largely on the severity

of the damage to the kidneys. All patients should have clearance tests to determine kidney capacity.

After the diagnosis has been established, the patient should be placed on a low calcium diet. The total calcium intake should be restricted to 50 mg daily. Vitamin D should not be given. Corticosteriods are helpful, especially during the first few weeks. [6] Cortisone decreases calcium absorption from the intestines and increases the excretion of calcium. Sodium sulfate may be added to milk to make less soluble calcium salts, ie., calcium sulfate. Enough sodium sulfate should be added to neutralize the milk calcium. EDTA has been used, especially in acute cases, and is effective.[5] However, since it is a toxic drug, it is not advised in all cases.

The patient whose case is presented here showed evidence of typical osteosclerotic changes of the skull, had significantly high vitamin A and carotin levels and typical "elfin face". Her symptoms began before she was given vitamin D and did not show any significant clinical improvement three months after vitamin D had been discontinued. The case history and clinical findings are typical of a severe case of idiopathic hypercalcemia.

Summary

The case of a 14 month old girl with idiopathic hypercalcemia is presented. The patient had the typical "elfin face", high serum calcium, vitamin A and carotin levels. Reserve alkalin was slightly low, but other serum electrolytes were within normal limits. Osteosclerotic changes were noted in skull x-rays, but these changes disappeared after one month of treatment. The kidneys showed moderate to severe damage since inulin and kreatinin clearance tests were low. The patient improved on a low calcium diet and cortisone therapy.

REFERENCES

1. Butler, N.R.: Generalized retardation, with renal impairment, hypercalcemia and osteosclerosis of skull, Proc. Roy. Soc. Med. **44**: 296, 1951.
2. Fanconi, G.: Über chronische störungen des calcium -und phosphatstoffwechsels im kindesalter, Schweiz. med. Wchnschr. **81**: 908, 1951.
3. Schlesinger, B. E., Butler, N. R., and Black, J. A.: Severe type of infantile hypercalcemia, Brit. Med. J. **1**: 127, 1956.
4. Bongiovanni, A. M., Eberlein, W. R., and Jones, I. T.: Idiopathic hypercalcemia of infancy, with failure to thrive, New Engl. J. Med. **257**: 951, 1957.

5. Smith, D. W., Blizzard, R.M., and Harrison, H. E.: Idiopathic hypercalcemia; A case report with assays of vitamin D in the serum, Pediatrics 24: 258, 1959.
6. Fellers, F. X.: Idiopathic hypercalcemia, in Gellis, S.S., and Kagan, B. M.: Current Pediatric Therapy, Philadelphia and London, W. B. Saunders, 1964, p. 332.
7. Shiers, J. A., Neuhauser, E. B. D., and Bowman, J. R.: Idiopathic hypercalcemia, Am. J. Roent. 78: 19, 1957.
8. Black, J. A., and Carter, B. R. E.: Association between aortic stenosis and facies of severe infantile hypercalcemia, Lancet 2: 745, 1963.
9. Beuren, A. J., Apitz, J., and Harmjanz, D.: Supravalvular aortic stenosis in association with mental retardation and a certain facial appearance, Circulation 26: 1235, 1962.
10. Williams, J. C., Barratt-Boyes, B. G., and Lowe, J. B.: Supravalvular aortic stenosis, Circulation 24: 1311, 1961.
11. Sinclair, H. M.: Essential fatty acids and idiopathic hypercalcemia of infancy, Lancet 1: 639, 1958.
12. James, A. T., Webb, J., Stapleton, T., and MacDonald, W. B.: Essential fatty acids and idiopathic hypercalcemia of infancy, Lancet 1: 502, 1958.
13. Fellers, F. X., and Schwartz, R.: Etiology of the severe form of idiopathic hypercalcemia of infancy. A defect in vitamin D metabolism, New Engl. J. Med. 259: 1050, 1958.
14. Hooft, C., Vermassen, A., and Blancquart, A.: Observation concerning the evaluation of the chronic form of idiopathic hypercalcemia in children, Hev. Paed. Acta 18: 138, 1963.
15. Rhaney, K., and Mitchell, R. G.: Idiopathic hypercalcemia of infants, Lancet 1: 1028, 1956.