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THE RESULTS OF SODIUM FLUORIDE TREATMENT IN OSTEOGENESIS IMPERFECTA

Nihat Bilginturan, M.D.*, and Şinasi Özsoylu, M.D.**

Osteogenesis imperfecta is a generalized disorder of the connective tissue, involving the skin, ligaments, tendons, fascia, sclera and inner ear, in addition to bone. It is a rare condition, characterized by fragility of the bones, leading to multiple fractures. Those with this disorder usually also have blue scleras and flaccid ligaments. Some become deaf in later life.

This syndrome has been given several names, some of which distinguish between the early and late forms of the disease. The terms in most general use are osteopsathyrosis idiopathica (Lobstein), osteogenesis imperfecta (Vrolik), fragilitas ossium (Gurlt). osteogenesis imperfecta congenita and osteoporesis imperfecta tarda (Looser).

Osteogenesis imperfecta is a hereditary defect of the bone matrix, and is associated with defective formation and differentiation of subperiosteal and endostal bone. Ruth[1] considered the probable causal mechanism to be diminished osteoblastic activity. According to Potter[2] the principle disturbance is in the excessive destruction of bone trabeculae already formed.

Two clinical types of the disease are well known: osteogenesis imperfecta tarda and osteogenesis inperfecta congenita. In the

From Ankara University Hacettepe Faculty of Medicine and Hacettepe Children's Hospital.

* Associate in Pediatrics.

** Pediatric hematologist and Assistant Professor of Pediatrics.

congenital form, the fractures may occur early, even *in utero,* and the infant may be born with deformed extremities as the fractures often heal in abnormal positions. This type was previously considered to be a non-hereditary or a recessively inherited disorder. However, recent publications about the incidence of congenital forms in consecutive siblings make it necessary to conclude that the inheritance of the congenital, as well as of the tarda form, is dominant.[3,4] After studying 55 families with 180 affected individuals, Seedorff[5] has suggested a multiple-gene theory as the cause of the tarda form of the disease in which the child appears normal at birth and fractures do not occur until after the first year of life.

Several kinds of treatment have been tried, but none to our knowledge has been beneficial in alleviating the condition. Although sodium fluoride treatment has produced some fairly good results, it is not in general use.[6]

The purpose of this paper is to present the results of sodium fluoride treatment in two patients with the disease.

Case Reports

Case 1. G. Y. (HCMC 64/41270), was first seen in the outpatient clinic of Hacettepe Children's Hospital when she was two months old because of deformities of her arms and legs. The history of pregnancy and delivery was uneventful. Deformed arms and legs were, however, noted immediately after birth. At the age of one and a half months, the child had a right humeral fracture which healed completely. There was no family history of bone disease, blue sclera or deafness. The parents and three year old sister of the patient were well and healthy. One sibling had died at the age of two months following milk aspiration.

Physical Examination : The patient was a small child with a soft skull and blue scleras. Both upper and lower extremities were severely deformed because of multiple fractures. X-rays of the extremities showed thinning of the cortex, ground glass appearance, and multiple fractures (Figure 1). X-rays of the skull revealed narrowing of the diploic space and numerous wormian bones (Figure 2).

At the age of six months the child was admitted to the hospital with complaints of fever, cough, diarrhea and vomiting. Following antibiotic treatment for bronchopneumonia, she was given sodium fluoride, five mg twice a day, for the treatment of her basic bone disease. At this time, the physical and x-ray findings were almost the same as reported previously (Figure 3). She was followed in the out-patient clinic at two month intervals. On her first visit, two months after the treatment was started, her daily fluoride intake was increased to 30 mg (15 mg twice a day). After eight months of treatment, x-rays of the

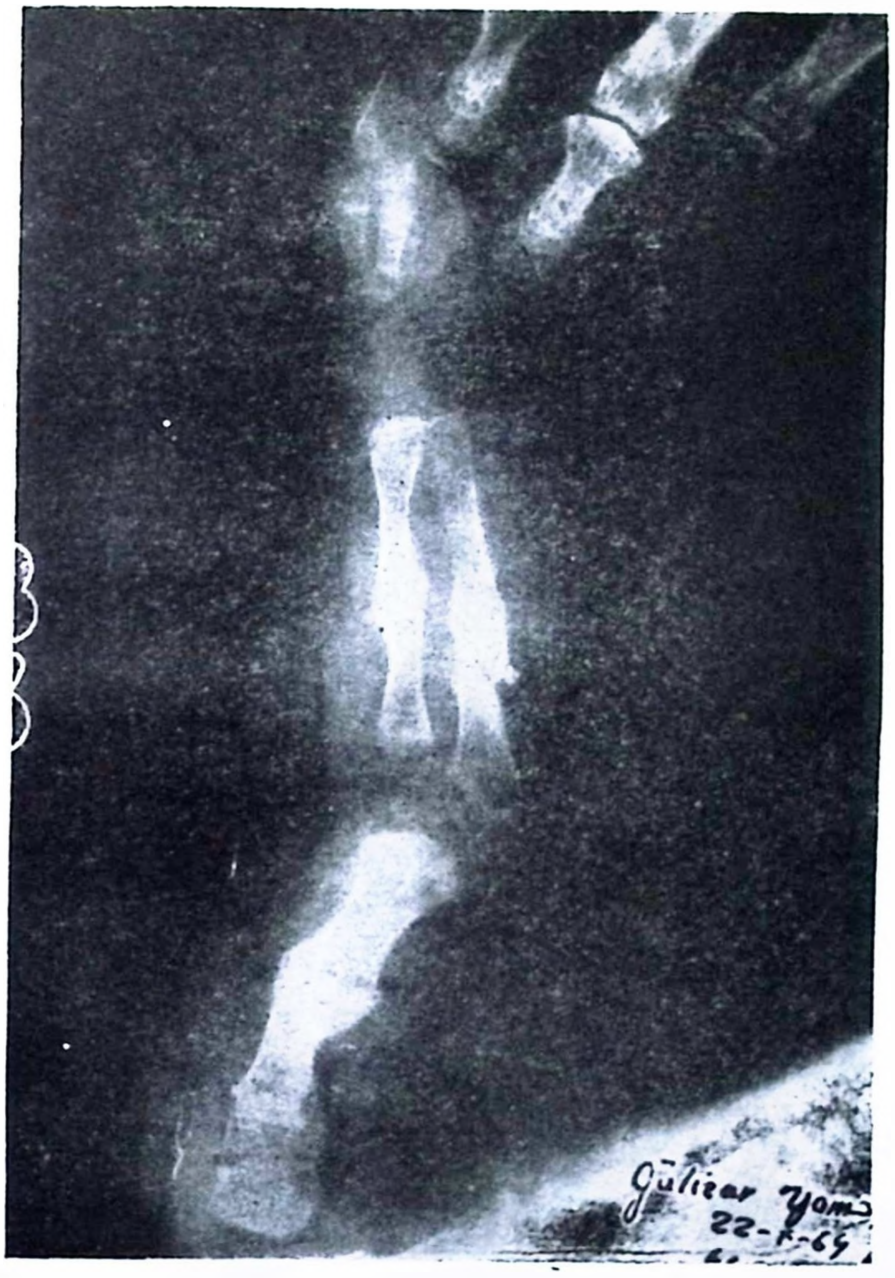

Figure 1. X-ray of the right arm, showing thinning of the cortex, ground glass appearance, and multiple fractures, patient two months old.

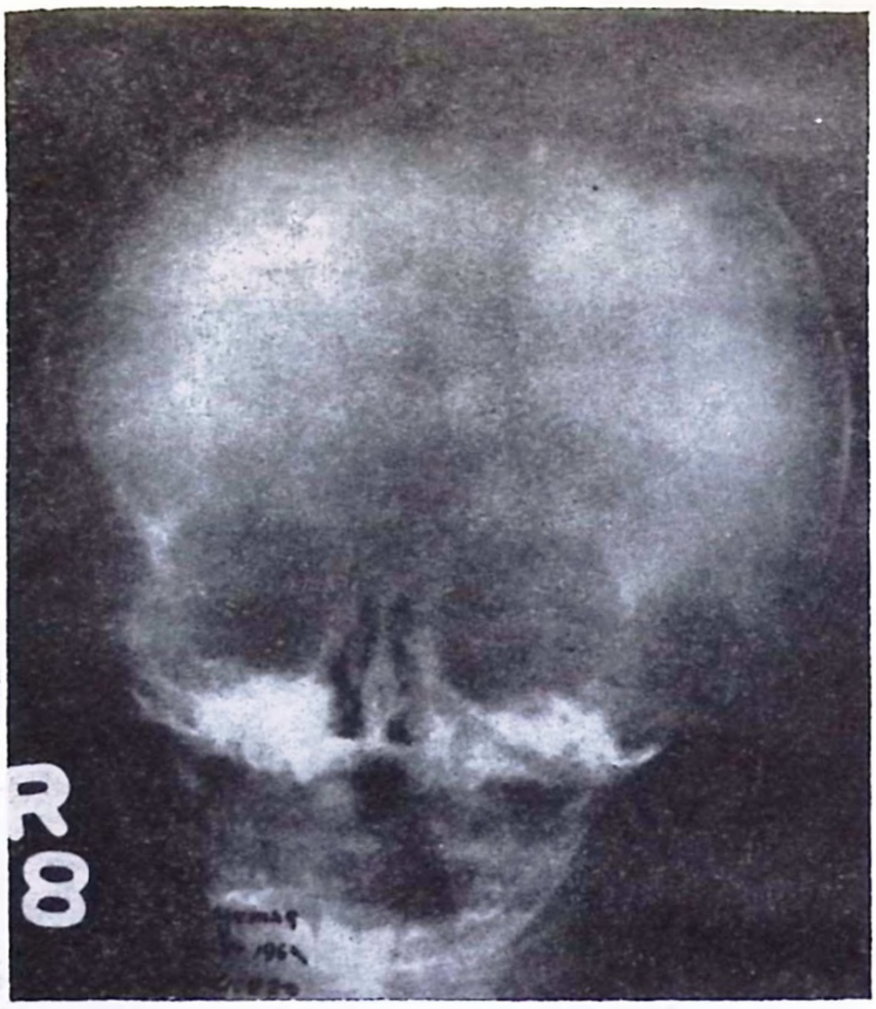

Figure 2. X-ray of the skull showing narrowed diploic space and numerous wormian bones, patient two months old.

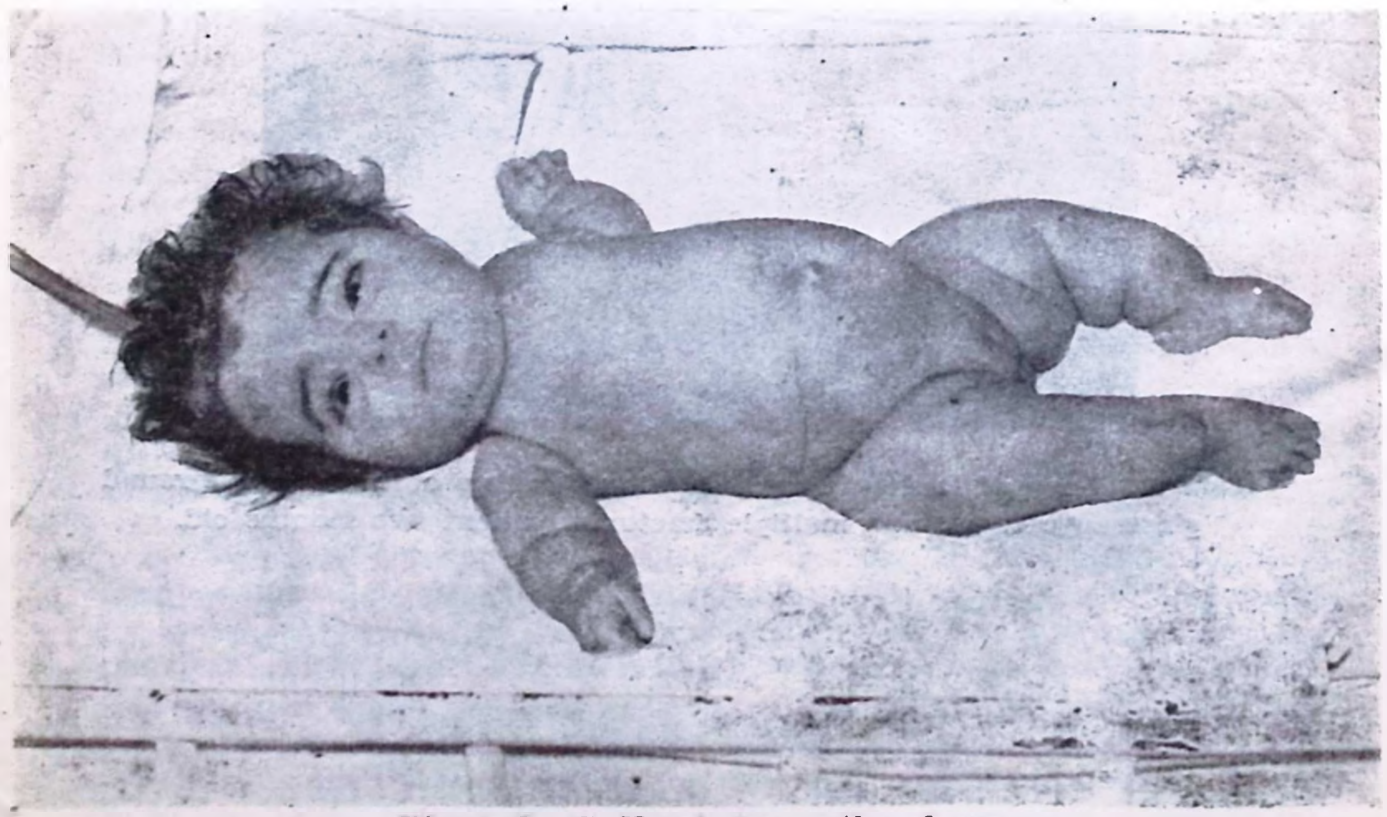

Figure 3. G. Y., at six months of age.

skull showed a slight thickening of the cortex with some widening of the diploic space (Figure 4). X-rays of the extremities revealed some thickening of the cortices, complete healing of the fractures and good medulla formation (Figure 5). She has been doing well, and no further fractures have been reported in spite of the fact that she has fallen once. She is still receiving the same daily dosage of sodium fluoride.

Case 2. N. A. (HCMC 65/30416) : This one and a half month old girl was brought to the out-patient clinic of Hacettepe Children's Hospital because of deformities of the extremities. The pregnancy was uneventful except for decreased fetal movements. The parents noted that the child had deformed extremities and softening of the skull at birth. There was no history of bone disease, blue scleras or deafness in the family. The patient's parents and two brothers were well and healthy.

Physical Examination : The child appeared to be hydrocephalic, with wide open anterior fontanel and blue scleras. Her lower extremities and left arm were severely deformed. Other physical findings were unremarkable.

Laboratory Examination : Her serum calcium level was 10 mg %; phosphorous, 5.2 mg %; alkaline phosphatase, 12.5 Bodansky units; VDRL, negative.

X-rays of the skull showed thinning of the cortex with depression of the occipital area, ground glass appearance and numerous wormian bones (Figure 6). X-rays of the extremities revealed thinning of the cortices, ground glass appearance of the medulla, and multiple fractures (Figure 7).

After the diagnosis of osteogenesis imperfecta congenita, treatment with sodium fluoride, 30 mg daily (15 mg twice a day) was begun. The patient has improved and no further fractures have been reported.

Two months after treatment with sodium fluoride, x-rays of the skull showed a slight thickening of the cortex, disappearance of the depression in the occipital area and some of the wormian bones (Figure 8). X-rays of the extremities revealed slight thickening and disappearance of the irregularities of the cortices, and healing of the fractures with good medulla formation (Figure 9). Radiological findings after five months of treatment with sodium fluoride are seen in Figure 10.

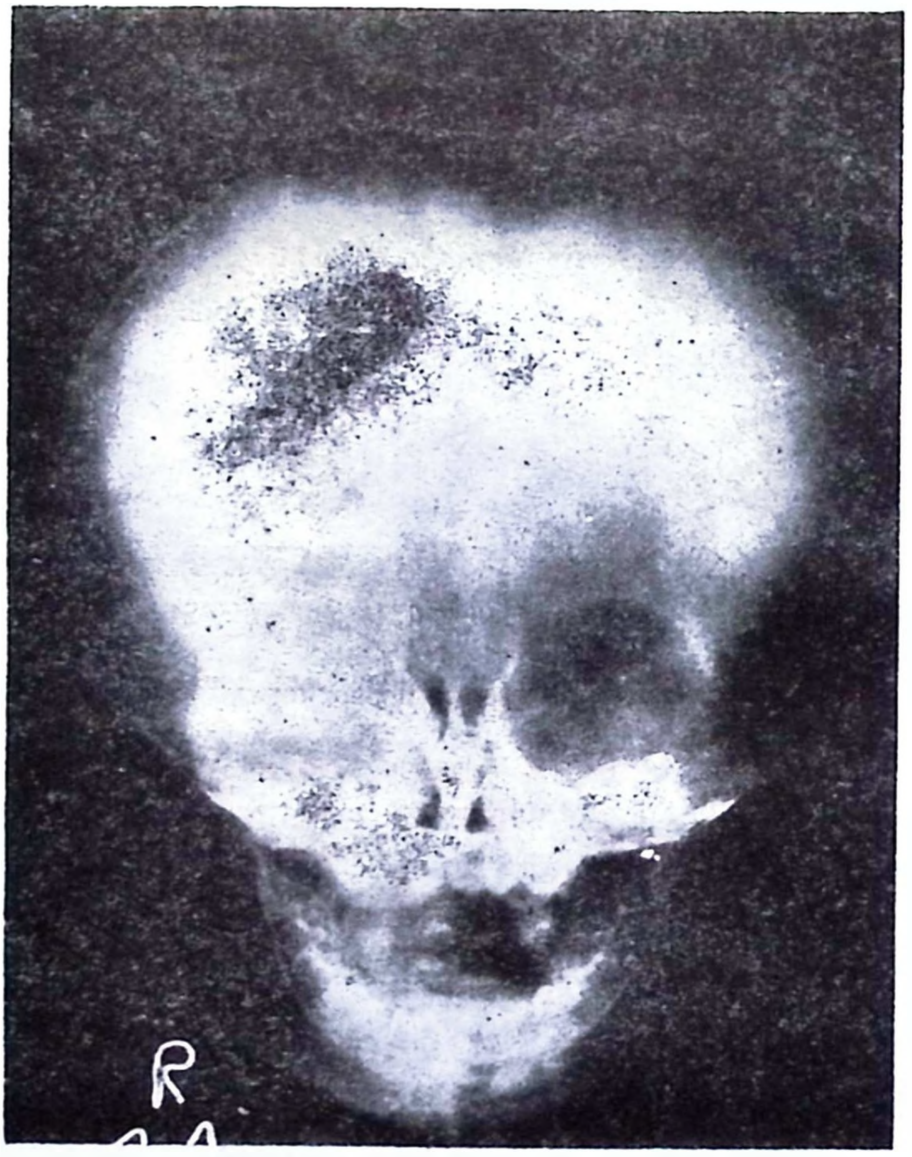

Figure 4. X-ray of skull after eight months of treatment, showing slight thickening of the cortex and some widening of the diploic space.

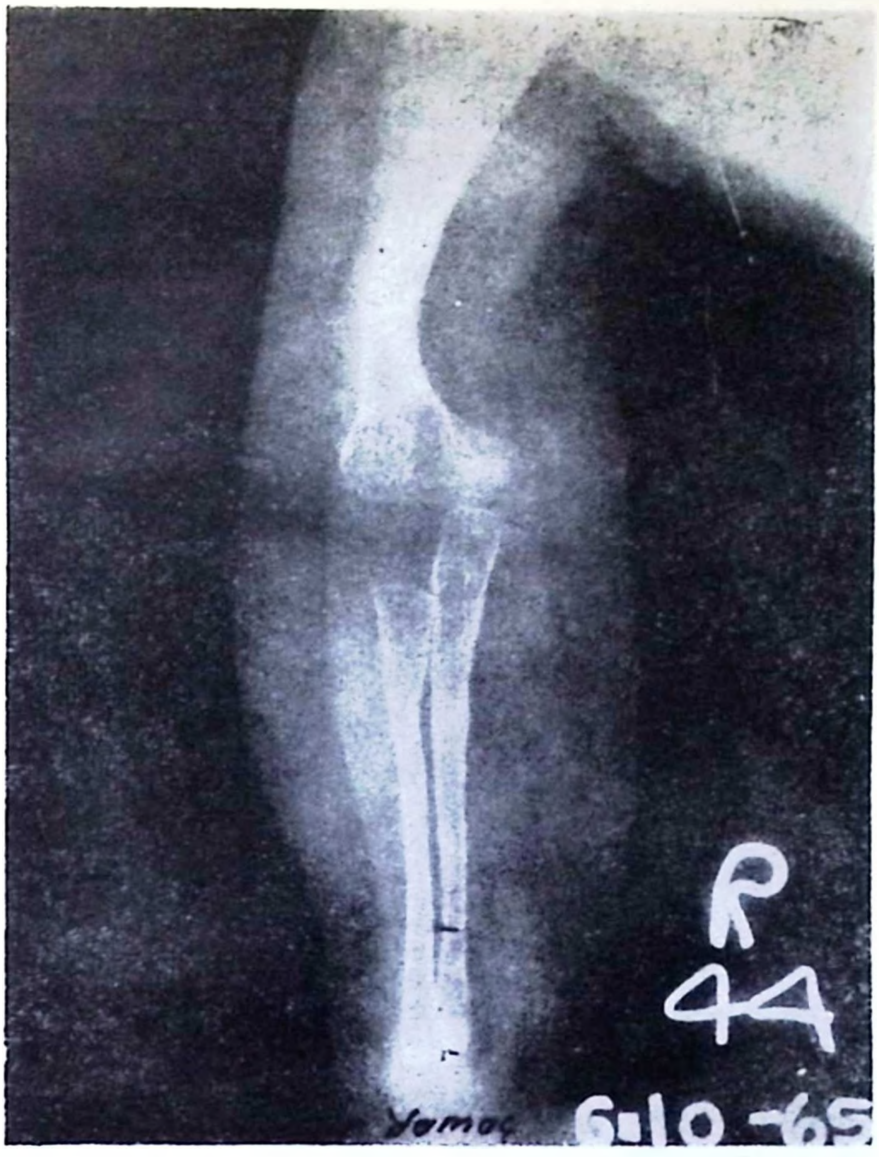

Figure 5. X-ray of right arm showing some thickening of the cortices, complete healing of the fractures and good medulla formation.

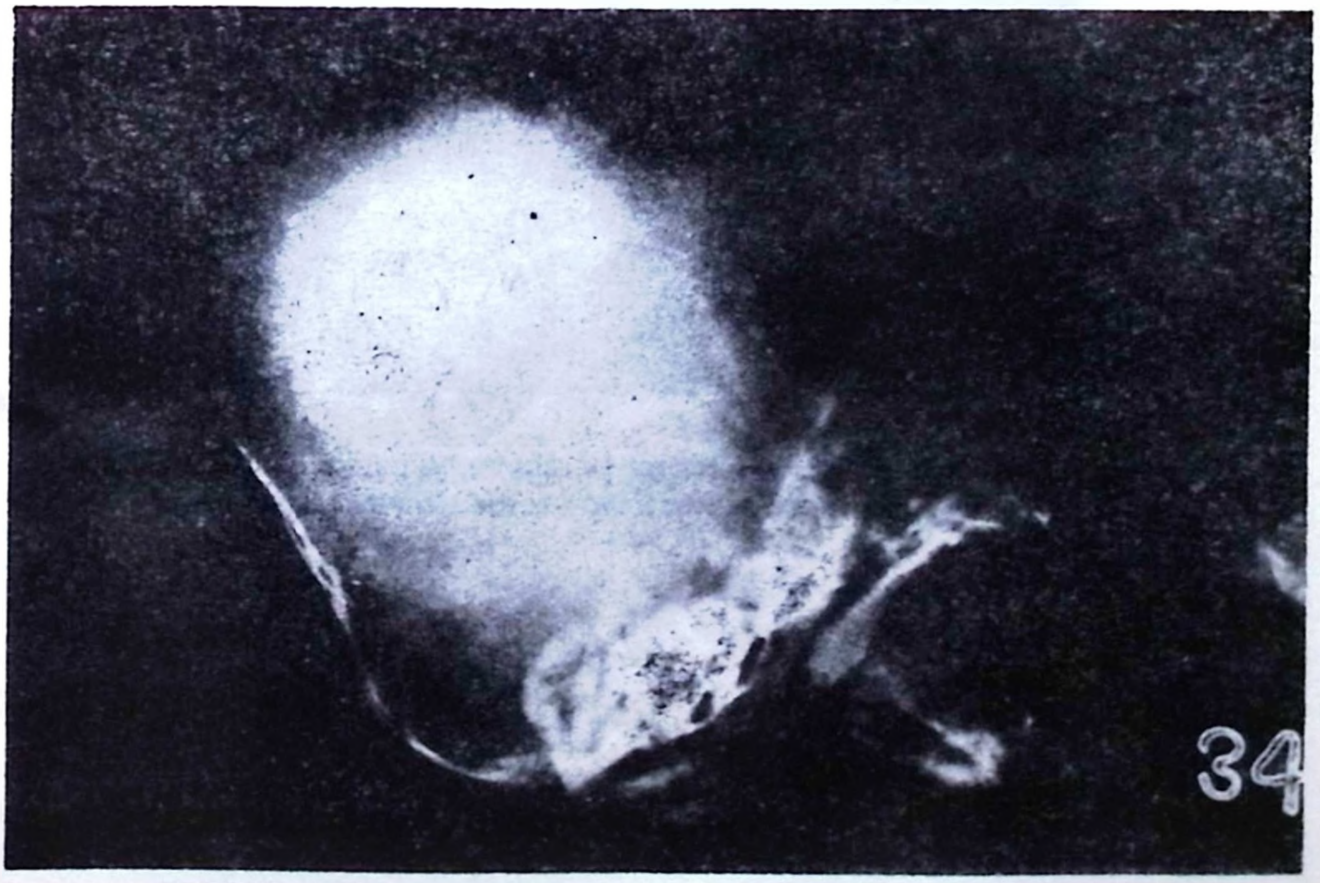

Figure 6. X-ray of the skull showing thinning of the cortex, depression of the occipital area and numerous wormian bones.

Figure 7. X-ray of the lower extremities shows thinning of the cortices, ground glass appearance of the medulla, and multiple fractures.

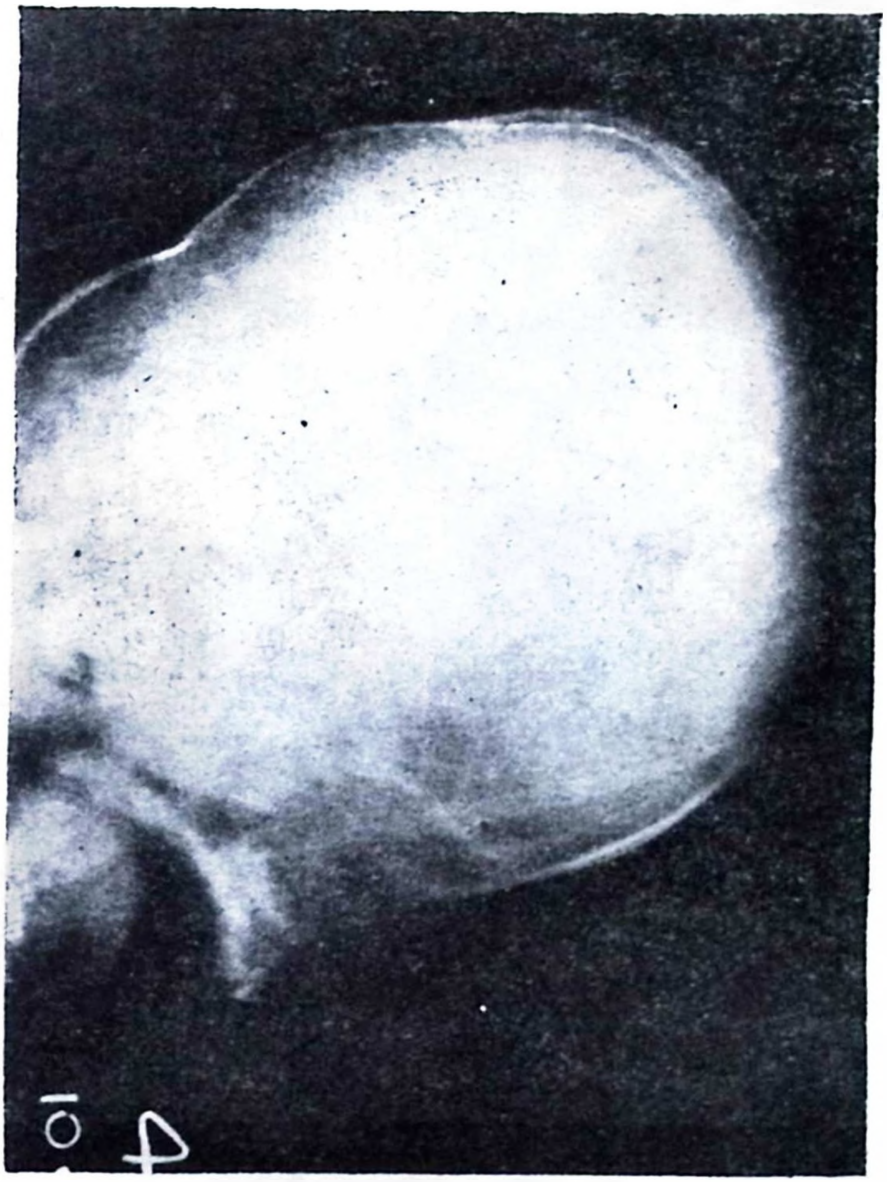

Figure 8. X-ray of the skull after two months of treatment shows slight thickening of the cortex, disappearance of the depression in the occipital area, and decrease in the number of wormian bones.

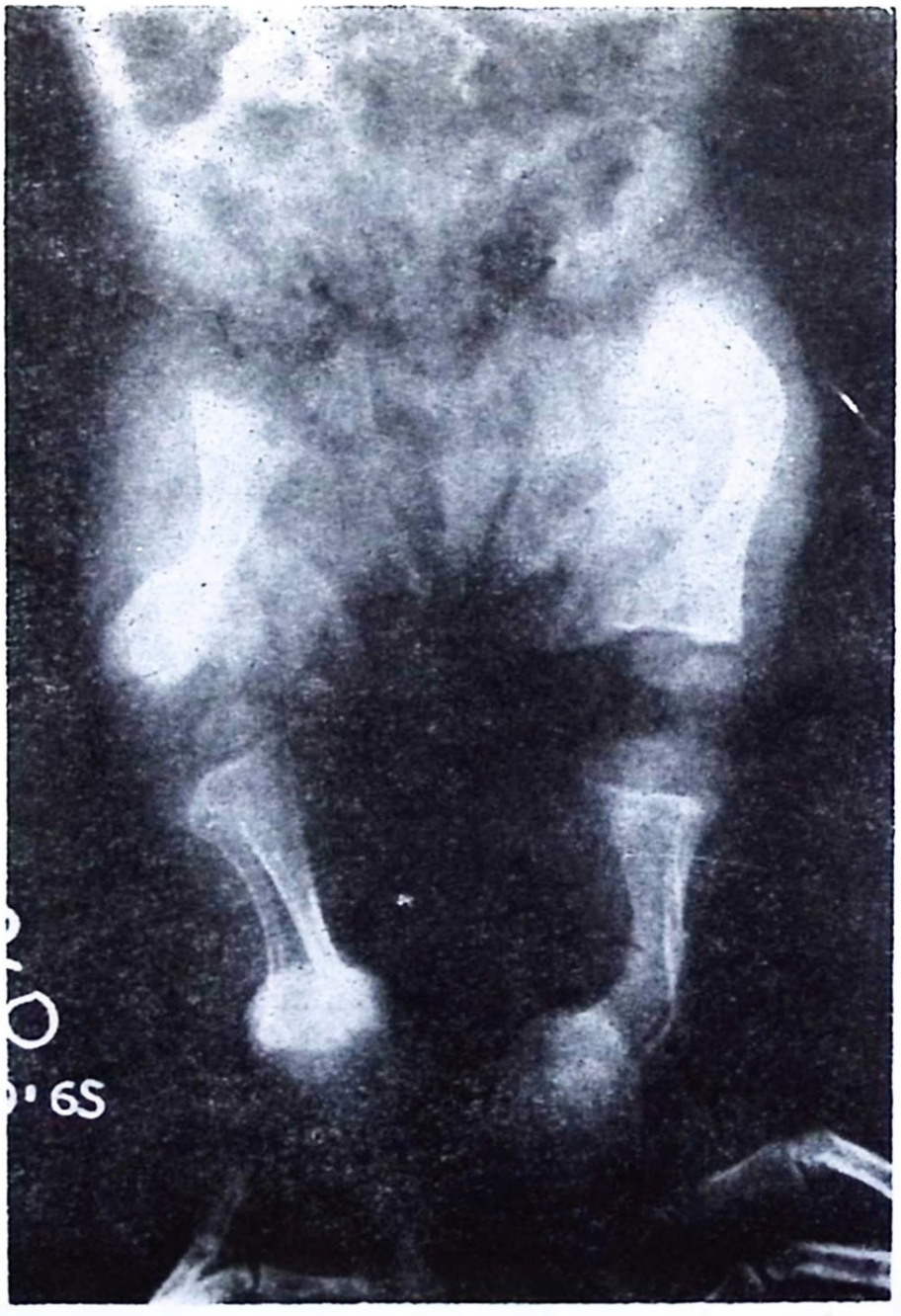

Figure 9. X-ray of lower extremities after two months of treatment shows slight thickening and more regular appearance of the cortices, and healing of fractures with good medulla formation.

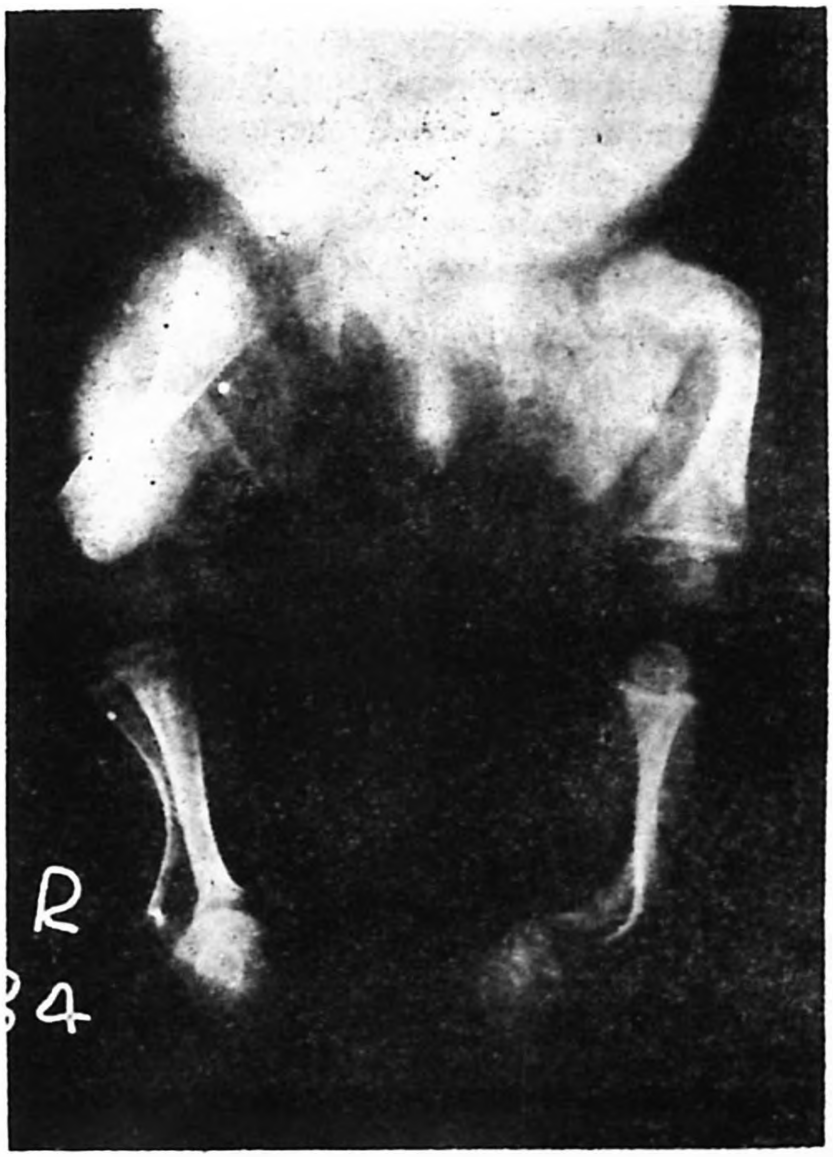

Figure 10. X-ray of lower extremities after five months of treatment.

Comments

No effective treatment for osteogenesis imperfecta has been established because the reason for the failure of normal development and maturation of collagen, characteristic of the disorder is yet to be determined. Early attempts to treat the disease included orthopedic correction of the deformities and improved diet, with high calcium, phosphate and vitamin D intake. Estrogens and androgens have also been used because clinical experience in man[7] and experimental evidence from animals[8], both indicate that these agents play an important role in normal formation of bone matrix.[9] Although serum albumin, which seems to be a precursor for bone matrix, has been given to patients with certain acquired varieties of osteoporosis, it has not been tried in the treatment of osteogenesis imperfecta.[10]

The effect of fluoride on the skeletal system was first described by Moller in 1932[11]. Following these observations, Roholm, in 1937, reported on a fairly large group of cryolite miners among whom 70 per cent had slight or moderate osteosclerosis.[12] Aside from minor gastrointestinal and joint symptoms, these people were asymptomatic. Later, Largent demonstrated that osteosclerosis can result from prolonged exposure to fluoride and that subjects with minimal or moderate osteosclerosis are usually asymptomatic and in apparent good health.[13] The above-mentioned observations suggested that salts of fluorine might be effective in treating patients with osteoporosis. Rich, Purves and Bernstein tried fluoride treatment on subjects with metabolic bone diseases and had good results.[14–16] Recently Rich and co-workers showed that calcium retention is brought about in most subjects who have been given one mg of fluoride (as an ion) per kg per day, for two or three months.[17]

Only two symptoms, epigastric distress and joint pain, have been associated with fluoride treatment. Epigastric pain usually occurs within one minute of ingestion and lasts about 30 minutes. It is more common among those patients who take more than 10 mg at a time. Distress decreases when fluoride is taken after a meal, and disappears when taken after ingestion of aluminium gel, calcium carbonate, or in enteric-coated tablets. Joint pain occurs in the knees or ankles on weight bearing. This symptom begins gradually after several months of treatment and persists unless the fluoride is discontinued.

The effect of fluoride seems to be to reduce the excretion of calcium in both urine and stool. It is not clear why there should be

stool calcium reduction in treated patients, but it may be a result of either increased gastrointestinal absorption or reduced excretion of endogenous calcium, or both.

We used a 2.4 per cent solution of fluoride, administered in dosages of 15 mg two or three times a day, in the treatment of our patients. One of these patients has been receiving this treatment for more than ten months and has not had any toxic symptoms. Although a degenerating course is expected in the congenital form of this disease, marked clinical and roentgenological improvement was observed in the cases reported here. Unfortunately, balance studies could not be carried out on either of these patients. Further studies will be reported in future articles.

Summary

This is a clinical and roentgenological report on the treatment of two infants with osteogenesis imperfecta with sodium fluoride. The drug was administered orally, and treatment has continued over a period of four to nine months with good clinical and roentgenological response. There have been no toxic reactions to the drug, and no reports of additional fractures since treatment was started. Both patients were given 15 to 30 mg fluoride per day (or three to six mg sodium fluoride per kg per day). No data on calcium retention during fluoride treatment was obtained.

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