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FURTHER EXPERIENCES WITH SODIUM FLUORIDE TREATMENT IN OSTEOGENESIS IMPERFECTA*

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Osteogenesis imperfecta is a hereditary condition which is characterized by bone fragility, blue sclera, and deafness. It is a complex disease with many variant forms and systemic manifestations and a wide range of clinical expressions[1]. This hereditary condition can be classified in two different forms: Osteogenesis imperfecta congenita representing lethal congenital cases with multiple antenatal intrauterine fractures, and osteogenesis imperfecta tarda with fractures occurring after birth, generally with a better prognosis. Osteogenesis imperfecta tarda is further subdivided according to the time of appearance and severity of the disease: tarda gravis (from birth to 1 year of age) and tarda levis (from one year on).

Various regimens have been proposed for the treatment of osteogenesis imperfecta. Because of the decreased absorption of calcium and phosphorus, Vitamin D has been tried without success, and it also carries the risk of hypercalcemia[1]. Since the fracture frequency decreases after puberty, estrogen and androgens have been used in treatment[2], with no clear effect. Since then magnesium oxide[3], vitamin C[4], and human growth hormone[5] have been tried without any apparent effects. Because of the inhibitory effect of calcitonin upon bone resorption, this hormone has also been tried in the treatment of osteogenesis imperfecta. Although favorable responses have been reported with calcitonin in relatively short-term studies[6-11], long-term treatment with this agent has proved to be beneficial in osteogenesis imperfecta tarda but not in the congenita form[12].

Aeshlimàn et al[13] and we[14] have reported striking improvement following administration of sodium fluoride in infants and young children with severe osteogenesis imperfecta. Although only a few reports[15,16] supporting the usefulness of this method of treatment have appeared in the literature, we nevertheless carried out a program of sodium fluoride treatment in these particular patients, and we would like to present our long-term results.

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TABLE I

Data on Patients with Osteogenesis Imperfecta

Duration of Follow-up	Names	Sex	Type of O. I.	Age at diagnosis	Age at start of treatment	Clinical improvement	X-ray improvement	Side effects
½ - 4 YEARS	G.Y.	F	Congenita	At birth	2 months	Moderate	Moderate	None
	M.A.	F	Congenita	At birth	1 month	Moderate	Moderate	None
	R.S.	M	Congenita	At birth	1½ years	Moderate	Slight	None
	N.C.	F	Congenita	3 days	1 month	Moderate	Slight	Vomiting
	S.Y.	F	Congenita	At birth	1½ years	Slight	Slight	None
	G.B.	F	Congenita	At birth	4 years	Moderate	Slight	Vomiting
	S.Y.	F	Gravis	7 days	9 months	Moderate	Slight	None
	O.E.	M	Gravis	15 days	3 years	Moderate	Slight	Nausea, vomiting
	M.C.	M	Gravis	3 months	3 years	Slight	Slight	None
	G.M.	F	Gravis	6 months	6 months	Slight	None	Vomiting
	M.A.	F	Gravis	6 months	1½ years	Moderate	Slight	None
	S.U.	F	Gravis	9 months	1½ years	Moderate	Slight	None
	A.T.	M	Gravis	1 year	2 years	Moderate	Slight	None
	M.T.	M	Levis	2½ years	6 years	Slight	Slight	None
	A.U.	M	Levis	2½ years	6 years	Slight	None	Vomiting
4 - 6 YEARS	S.T.	F	Congenita	At birth	15 days	Moderate	Slight	Gingival hypertrophy
	O.E.	M	Gravis	8 months	1 year	Slight	Slight	None
	A.S.	M	Gravis	1 month	1 year	Good	Good	None
4 - 8 YEARS	B.A.	F	Gravis	11 months	11 months	Excellent	Excellent	None
	S.K.	M	Levis	6 months	10 months	Moderate	Slight	None

Material and Methods

Twenty patients with osteogenesis imperfecta (9 males and 11 females, aged between 15 days and 8 years) have been followed at the Hacettepe Children's Hospital from six months to eight years. Seven of the patients had the osteogenesis imperfecta congenita type and thirteen the tarda type; ten of the latter had the gravis and three the levis form of the disease (Table I).

All the patients had x-rays of the skull and of the long bones of the same side at the beginning of treatment and at intervals of three to six months. Almost all patients had at least one serum calcium, phosphorus and alkaline phosphatase determination before treatment. Following the diagnosis of both forms of osteogenesis imperfacta the patients were placed on sodium fluoride 4-5 mg/kg/day as a 2.4% solution in 2 to 4 divided doses, preferably after meals.

The effect of the treatment was evaluated on the basis of clinical responses and radiological improvements. The clinical evaluation of response to treatment was graded according to the disappearance of crying, increase in overall activity, and absence of new fractures. Radiological evaluation of response to therapy was based on the changes in bone density, the thickness of cortical bones, the regularity of the contours of the secondary ossification centers in the epiphysis, and the healing of the fractures.

Results

Regardless of the clinical form of the disease, congenita or tarda, including the gravis and levis forms, all the patients demonstrated a good clinical response to the treatment (Table I). On the whole, activity of the patients increased, crying stopped and no further fractures occurred. Radiologically 90% of the patients demonstrated slight to marked improvement (Figures 1-3).

Especially in two cases, the response to the treatment was so excellent that one cannot suspect the disease from their recent x-rays (Figures 4,5). In spite of the clinical improvement in 10% of the patients, the radiological appearance of the bones did not change, probably as a result of irregular and/or inadequate use of medicine. No serious side effects of the treatment were encountered in any of the patients (Table I).

Discussion

Osteogenesis imperfecta is a congenital disease of the bones with varying severity, characterized by frequent fractures. Other stigmata associated with the disease are blue sclera, lax joints, impaired hearing, thin skin, and dental abnormalities. All abnormalities are related to the structural abnormalities of collagen in the skin, bones and sclera of the patients[17-19].

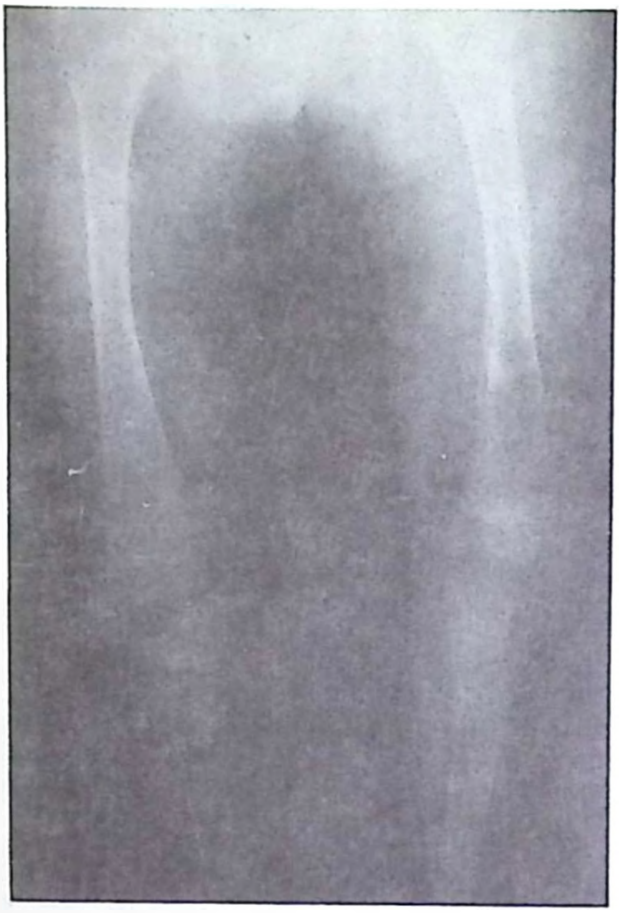


Figure 1.

Generalized osteoporosis and multiple fractures of both femurs at the beginning of treatment at 11 months of age (B.A.).

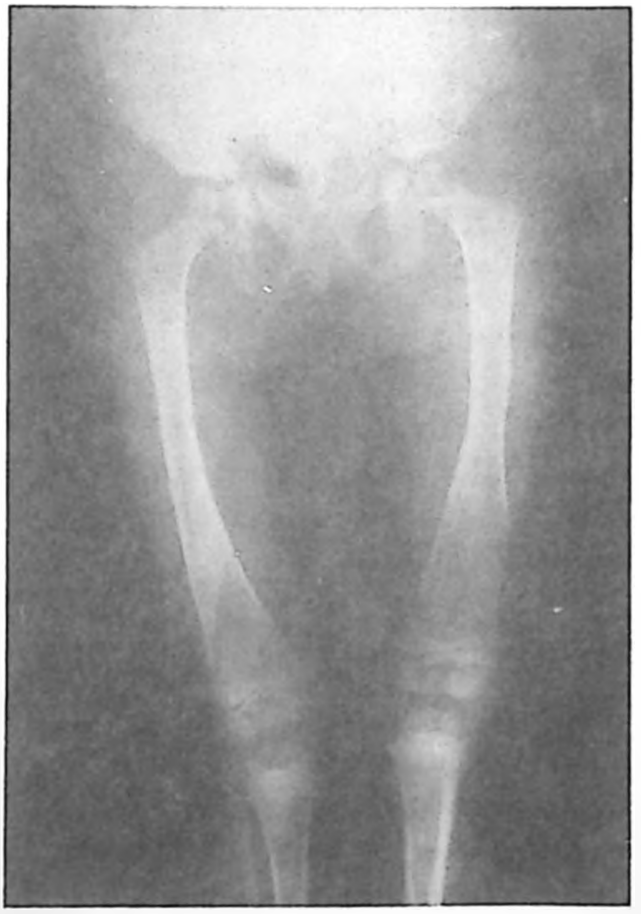


Figure 2.

X-ray of the above patient after six months of treatment, showing healing of the old fractures.

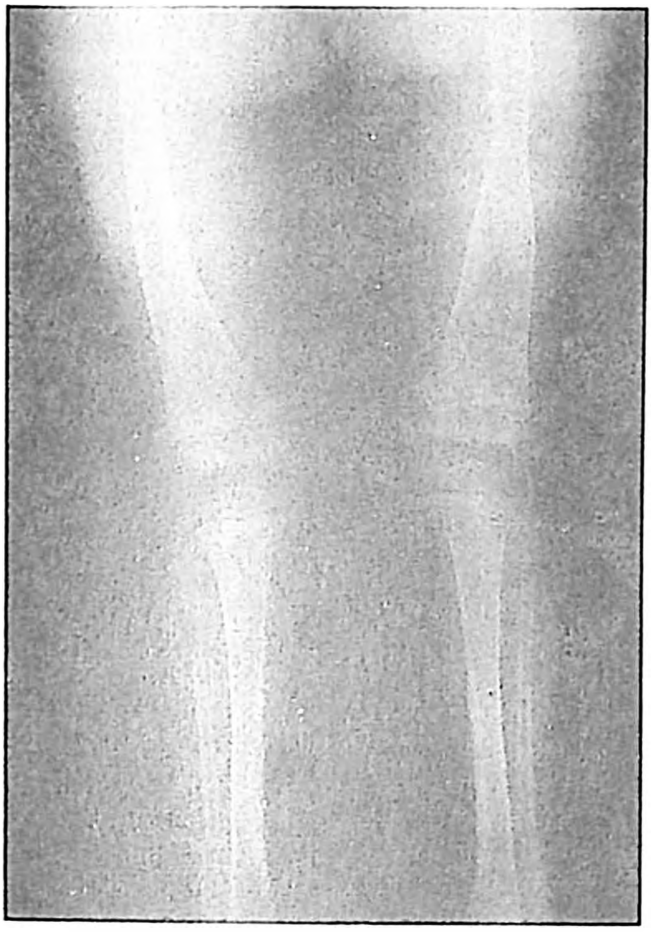


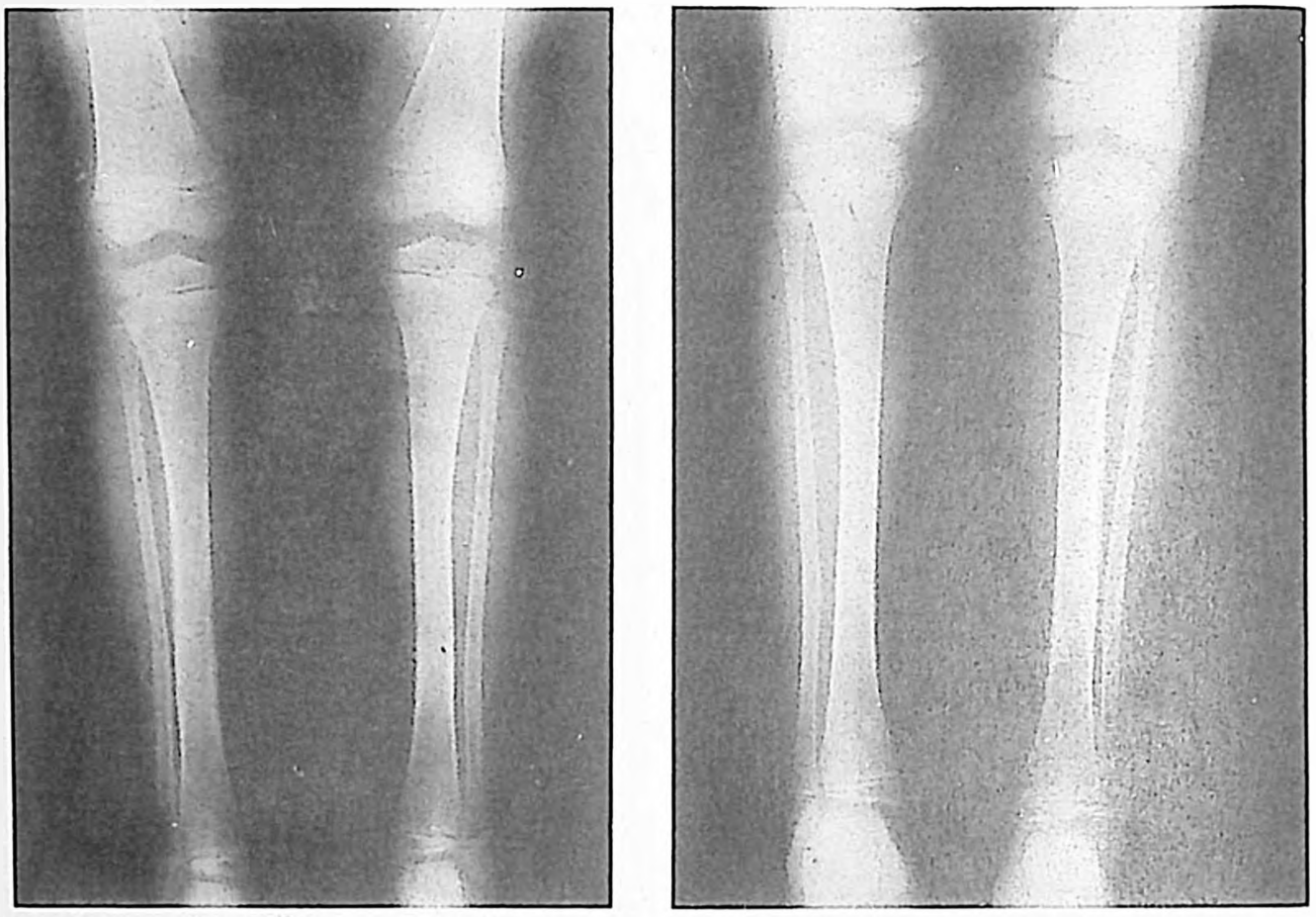
Figure 3.

X-ray of the same patient after 1 year of treatment; bones are normal with the exception of slight widening in the left femur at the site of old fracture.

Because of the defective formation of subperiosteal and endosteal bone, the fractures may occur very early, in the uterus or in early infancy (congenita form), or in late infancy or early childhood (tarda form). At least seven of our patients had the congenita type, 10 the gravis type and the rest the levis type of the tarda form. After-fluoride treatment all of the patients with the congenita form showed moderate or slight improvement clinically and radiologically. The response to treatment in the gravis form was graded as excellent and good in two patients both clinically and radiologically. Clinical improvement was more prominent than the x-ray findings in this form. The response to treatment was less clear in the levis form.

Four to 5 mg/kg/day of sodium fluoride was administered orally as a 2.4% solution by dividing the daily amount into two to four doses. Each dose was given immediately after feeding. In five patients in whom the results of treatment were the least satisfactory, vomiting was a side effect of the treatment. We were not sure how much fluoride should be administered in those patients. Gingival hypertrophy was observed in one of the patients. The rest of the patients tolerated sodium fluoride administration well and responded to the treatment.

Since this treatment is inexpensive, easily available and can be given without many side effects for a long period of time (up to 8 years), it should be tried in all patients



Figures 4 & 5.

The same patient's X-ray 3 and 4 years after treatment, indicating almost completely normal bones.

with this disorder. Unfortunately neither bone histology nor balance studies could be carried out in our patients.

Summary

Twenty patients with osteogenesis imperfecta (seven with congenita and 13 with tarda type) aged between 15 days and 8 years were treated with sodium fluoride for periods of from 6 months to 8 years. Effects of treatment were evaluated on the basis of clinical improvement (disappearance of crying, increase in overall activity and absence of new fractures) and radiological changes (increase in bone density, thickness of cortical bones, regularity of the contours of the secondary ossification centers in the epiphysis).

All the patients demonstrated good clinical improvement regardless of the clinical type of the disease. Radiologically 90% of the patients showed slight to marked improvements. No serious side effects were encountered in any of the patients.

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