Long-term administration of antiepileptic drugs and the development of rickets

Two young children developed rickets as a complication of anticonvulsant therapy and were subsequently cured by vitamin D therapy. They are the youngest patients thus far reported, and the first to be reported in the United States. On the basis of clinical studies, rickets and osteomalacia can be added to the list of toxic effects of anticonvulsant therapy. Although the exact mechanism of pathogenesis remains to be elucidated, it appears likely that these drugs alter the metabolism of vitamin D in certain patients. Special attention should be paid to the status of calcium and phosphorus metabolism in children who are receiving such drugs, and to their intake of vitamin D.

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The relationship between therapy with antiepileptic drugs and the development of rickets and osteomalacia has recently been the subject of investigations by several authors1-6 in Germany and England. There are no experiences reported from the United States. We are reporting two young children with debilitating neurologic illnesses who, during the course of long-term anticonvulsant therapy, developed clinical rickets. Both children are patients in our Pediatric Neurology Clinic and are the only cases of rickets we have recognized in this clinic during the 10 year period from 1960 to 1970.

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CASE REPORTS

Case 1. Patient C. H., a Caucasian girl, was the product of the mother’s fourth normal pregnancy and delivery. The first female child was normal. The second female child was mentally retarded but without clinical stigmata of tuberous sclerosis. The third child (a male) had a speech defect and poor coordination but average intelligence. Both parents and all four children are of normal height.

At two months of age Patient C. H. developed left-sided seizures which later became generalized. At the time of her first admission to the hospital at three months of age, physical and neurologic examinations, skull films, spinal fluid, echoencephalogram, and blood glucose were all normal. Bilateral subdural taps yielded no fluid. The electroencephalogram showed paroxysmal slow waves primarily seen over the left hemisphere.

Treatment with phenobarbital was begun at two months of age, and diphenylhydantoin was
added at three months. She developed depigmented nevi over the extremities and trunk in the first year of life, and psychomotor retardation was obvious by nine months of age. Because the seizures were uncontrolled, ethosuximide was added to the medication regimen at 11 months of age. She developed myoclonic seizures at nine months of age with a typical hypsarrhythmic electroencephalographic pattern and received a course of adrenocorticotropic hormone (starting with 40 units daily and then gradually diminishing doses over a 4 month period).

At two years of age, a yellowish pale lesion surrounded by pigment was noticed between the optic disc and the macula of the left eye. Tests for cytomegalic inclusion disease, rubella, histoplasmin, and toxoplasmosis were all negative.

At 2½ years of age, the mother noted enlargement of the wrists and ankles, and the examining physician detected enlargement of the costochondral junctions. The clinical diagnosis of rickets was confirmed by skeletal roentgenograms (Fig. 1), and the finding of reduced serum phosphorus, slightly low serum calcium, and elevated serum alkaline phosphatase concentrations.

Additional laboratory studies at that time revealed a serum albumin of 4.3 Gm., serum globulin 2.0 Gm. per 100 ml., and urea nitrogen 8 mg. per 100 ml.; the urine contained no albumin or glucose and had a pH of 7.0; the blood hematocrit was 40.5, the white blood count was normal, and the erythrocytes appeared normal on smear. The urinary amino acid pattern was normal on 2 dimensional paper chromatography. The stools were grossly normal.

In retrospect it should be noted that serum calcium and phosphorus were normal at three months of age, and that a chest roentgenogram taken at one year of age showed no evidence of abnormalities of the ribs or upper humeri.

In view of the fact that the child had been given a regular daily vitamin D supplement of 400 units, in addition to vitamin D-fortified milk, we felt that a diagnosis of nutritional rickets was unlikely. Nevertheless vitamin D was prescribed in a dose of 2,000 units daily, together with 150 mg. of elemental calcium as the gluconate salt. Since there was no response in serum phosphorus at the end of one month the diagnosis of resistant rickets was considered, and the dose raised to 50,000 units daily. Fig. 2 shows the favorable response to this therapy.

Fourteen months later (at age 3½ years) the mother, without consulting us, stopped giving vitamin D; after another eight months had passed, it was found that the serum phosphorus had dropped to 3.8 mg. per 100 ml. and the alkaline phosphatase had risen slightly, to 20 Bodansky units. Resumption of vitamin D therapy was followed by a rise in serum phosphorus and a fall in alkaline phosphatase. At age 5½ years the...
the mother once again discontinued vitamin D therapy, and as shown in Fig. 2 the serum calcium and phosphorus values subsequently decreased.

Sebaceous adenomata appeared on the face at four years of age. At the time of her last hospital admission in June, 1970 (5½ years old), she presented as a severely retarded child who had poor coordination and an unsteady gait. Speech was incoherent and she was unable to perform simple tasks. Skull films showed no evidence of intracranial calcification; however, the pneumoencephalogram showed small tubers projecting into the lateral and third ventricles. Brain scan (99mTc) was normal, as was the cerebrospinal fluid. Our final diagnosis was tuberous sclerosis associated with convulsive disorder and severe mental retardation.

Skeletal roentgenograms show, in addition to healed rickets, several focal radiodense lesions and one circumscribed radiolucent lesion in the first left metacarpal (Fig. 1), all of which are compatible with tuberous sclerosis.

The timing of the various medications, none of which was effective in controlling seizures, is shown in Fig. 2. Doses were as follows: phenobarbital 50 to 150 mg. daily, diphenylhydantoin 60 to 150 mg. daily, ethosuximide 250 to 375 mg. daily, primidone 150 to 375 mg. daily, and mephobarbital 96 mg. daily.

Case 2. Patient T. D., a Negro girl, was the product of the mother’s second pregnancy, during which she was exposed to German measles in the first trimester and did develop a rash. The mother’s first pregnancy terminated at five month’s gestation in the birth of a stillborn male fetus. At the time of birth, the one-minute Apgar score of Patient T. D. was five. The obstetrician had difficulty extracting the shoulders after the head and a left-sided Erb’s palsy was noticed. Birth weight was 4,000 Gm., length was 54 era., and head circumference was 35.5 cm.

At the end of the first year, microcephaly and psychomotor retardation were documented. At 13 months of age head circumference was 44 cm., height was 79 era., and weight was 10.3 Kg. Her rubella titer was 1:16, and that of her mother was 1:64.

Tonic-clonic seizures probably had started shortly after birth, but these were not brought to the pediatrician’s attention until one year of age. At that time the skull films were normal except for the small size of the skull. Electroencephalogram showed paroxysmal slow waves
and spikes particularly prominent in the mid-temporal regions. Treatment with phenobarbital and diphenylhydantoin was begun, but seizures were poorly controlled in spite of the addition of diazepam. At the present time she is still having 4 to 5 seizures daily; she is unable to walk, her speech is incoherent, and her movements are incoordinated. The course of her anticonvulsant medication is shown in Fig. 3. Doses were as follows: phenobarbital 64 to 128 mg. daily, diphenylhydantoin 75 to 100 mg. daily, diazepam 2 mg. at bedtime, trimethadione 600 mg. daily, and primidone 250 to 375 mg. daily.

At 4½ years, her mother noted enlargement of the wrists and ankles. Examination revealed, in addition, a mild genu valgum and enlargement of the costochondral junctions. The clinical diagnosis of rickets was confirmed by skeletal roentgenograms (Fig. 4) and reduced serum calcium and phosphorus values together with an elevation of the serum alkaline phosphatase.

Other investigations at this time revealed a serum albumin of 4.4 Gm. per 100 ml., serum globulin 2.6 Gm. per 100 ml., and blood urea nitrogen 7 mg. per 100 ml. The urine was negative for albumin and glucose, pH 8.0, and the amino acid pattern was normal on 2 dimensional paper chromatography. A 24 hour sample of urine contained 4 mg. of calcium and 38 mg. of phosphorus. The blood hematocrit was 41, white blood count was normal, and the erythrocytes appeared normal on smear; serum sodium, potassium, chloride, and CO₂ values were all normal.

The dietary history revealed that she had received a vitamin D supplement during the first year of life and for a brief period at about 2½ years of age, and that she had received vitamin D–fortified milk. There was no history of steatorrhea.

The possibility of nutritional rickets was entertained, and treatment with 400 units of vitamin D daily was begun. Since this produced no change in serum calcium, phosphorus, or alkaline phosphatase and no roentgenographic evidence of healing, calcium (135 mg. per day as the gluconate) was added, and the dose of vitamin D was increased in stepwise fashion,
DISCUSSION

In 1965, Wright reported elevated serum alkaline phosphatase values in 10 per cent of adult patients receiving Trinuride, which is a mixture of phenylethylacetylsulfate, diphenylhydantoin, and phenobarbitone. An incidence of 16 per cent was reported by Vas and Parsonage among adult patients in whom Phenturide had been added to a treatment regimen which included phenobarbitone, Phenytoin, primidone, Methoin, and sulthiame. In 1968 Kruse drew attention for the first time to the occurrence of rickets as a complication of long-term antiepileptic therapy in children. In a personal communication to us, he stated that he had seen 11 cases in children, aged 7 to 15 years. In his patients serum calcium was normal or slightly decreased, serum phosphorus was low, and serum alkaline phosphatase was elevated; skeletal roentgenograms were characteristic of rickets. Two of the children had tuberous sclerosis.

In 1970, Dent and associates reported four patients, aged 16 to 61 years, with osteomalacia in association with anticonvulsant therapy; in two of these the diagnosis was confirmed by bone biopsy. Richens and Rowe found that 29 per cent of a group of 160 adult patients at a residential treatment center for epileptic patients had elevated serum alkaline phosphatase levels and that 22 per cent had levels of serum calcium less than 9 mg. per 100 ml. A recent survey of institutionalized adolescent patients with epilepsy by Hunter and associates revealed that 30 per cent had a reduced serum calcium level, and 24 per cent had an elevation in serum alkaline phosphatase; however, their report did not include an evaluation for the presence or absence of rickets. Stößmann reported disturbances of ossification in 18 of 81 children under treatment for epilepsy; in four of these the roentgenographic appearance was consistent with rickets. Several authors state that the likelihood of these abnormalities is a function of the dose and duration of anticonvulsant medications. Since many patients had been treated with a combination of drugs it was not possible to incriminate any one particular drug. In the rat, on the other hand, Clark and associates could not induce rickets with Dilantin; other anticonvulsant drugs were not studied.

Although the pathogenesis of the disturbed
mineral metabolism is not known, the most likely possibility is that the anticonvulsant drugs interfere with the metabolism of vitamin D. Recent work has shown that this vitamin, once it has entered the body either in diet or through activation of cutaneous provitamin D by sunlight, undergoes a series of transformations: conversion to 25-hydroxycholecalciferol (25-HCC) in the liver, and further conversion to 1, 25-dihydroxycholecalciferol (1, 25-HCC) in the kidney. It is the latter compound which is the metabolically active form of the vitamin and hence responsible for effects on intestinal mucosa and on bone.

Kruse found low levels of vitamin D (1.5 and 2.5 μg per 100 ml. of serum) in two of his patients. Hahn and associates reported decreased plasma levels of 25-HCC in adult patients who were being treated with Dilantin and phenobarbital (14 ng. per milliliter compared to 20 ng. in control subjects). Since these two drugs are known to enhance hepatic enzyme activity, Dent and associates and Richens and Rowe have suggested that they may act to accelerate the degradation of vitamin D. Support for this hypothesis comes from the work of Hahn and associates, who found that phenobarbital accelerates the conversion of vitamin D₂ to inactive metabolites by rat liver microsomes. Recently, Hunter and associates have found that almost all children receiving anticonvulsant drugs excrete excessive amounts of d-glucaric acid in the urine, and they interpret this finding as indicative of hepatic enzyme induction.

With regard to the other reported nutritional defect associated with anticonvulsant drug therapy, namely, folate deficiency with or without macrocytic anemia, several possibilities have been considered. Klipstein found an accelerated clearance of folate in several of his patients and considered the possibilities of competitive inhibition or decreased plasma protein binding. Absorption of folate from the gastrointestinal tract appeared to be normal.

The dose of vitamin D necessary for the treatment of these patients has varied. Kruse found that 400 to 800 units per day was sufficient for his patients; Dent and associates used a daily intravenous dose of 50 μg of vitamin D₂ (equivalent to 2,000 units) plus ultraviolet radiation. The requirement for one of our patients (Case 1) is the range of 2,000 to 50,000 units, and is approximately 10,000 units in the other one. Both developed clinical rickets while receiving an estimated 200 to 800 units daily. It may be significant that the case reports thus far have all come from Great Britain and Germany where vitamin D–supplemented foods are not used to the same extent as in the United States. It would be of interest to survey epileptic children in this country.

With regard to our patients, it may be claimed that the association of anticonvulsant therapy and rickets was coincidental. The obvious way to have proved a causal relationship would have been to discontinue drug therapy while continuing the usual prophylactic dose of vitamin D, but the clinical status of neither patient would permit this. However, we do have reasonably good evidence that neither suffered from any of the other known forms of rickets. Simple deficiency rickets should have responded to a smaller dose of vitamin D than we found necessary to use; there was no evidence of renal or gastrointestinal tract disease; the lack of family history of short stature, the low values for serum calcium, and the occurrence of healing on rather modest doses of vitamin D all speak against the diagnosis of familial vitamin D-resistant rickets. Patients with pseudodeficiency rickets usually have evidence of disease in infancy, at an earlier age than ours; muscle hypotonia is a prominent feature, and many patients have lower levels of serum calcium than ours.

Of further interest is the fact that one of our patients, one of Stögmann’s four patients, and two of Kruse’s 11 patients have tuberous sclerosis. The skeletal lesions of tuberous sclerosis, which were predominantly osteoblastic and comparable to those described by Komar and associates, became evident in our patient (Case 1) after the rickets had healed.
ADDENDUM

Since submission of this paper for publication we have seen three additional children with rickets associated with antiepileptic drug therapy: a 2-year-old girl who had been treated with Dilantin and phenobarbital from age 6 months, a 16-month-old boy on similar medication from shortly after birth (both patients of Dr. Frederick Horner), and an 8-year-old girl who had been treated with Dilantin, phenobarbital, and Mysoline from one year of age (patient of Dr. Joseph Incavo). This first patient had had an adequate intake of vitamin D, whereas that of the other two was marginal (200 to 250 units daily). They are currently under treatment with vitamin D.

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REFERENCES


APPENDIX

Generic and common names for the drugs referred to:

diphenylhydantoin—Dilantin
ethenosuximide—Zarontin
diazepam—Valium
primidone—Mysoline
mephobarbital—Mebetal
phenylethylacetylucrea, diphenylhydantoin,
phenobarbitone—Trinuride
phenylethylacetylucrea—Pheneturide
adrenocorticotropin—Acthar-gel
trimethadione—Tridione