Rickets associated with anticonvulsant therapy in children with tuberous sclerosis

Rickets (or osteomalacia) is well known to occur in patients taking long-term anticonvulsant therapy (Kruse, 1968; Dent et al., 1970; De Luca, Masotti, and Partington, 1972; Silver et al., 1974; Hahn et al., 1975; Borgstedt et al., 1972) but the occurrence of this complication in tuberous sclerosis has been commented on only once (Borgstedt et al., 1972). This paper reports this occurrence in 5 children seen in the general paediatric unit of this hospital in the past 5 years.

Case reports

Case 1. A 15-year-old girl with severe mental retardation, a long history of seizures, marked adenoma sebaceum, and many cutaneous white macules was referred from the orthopaedic clinic, where she had attended with fractures of the left radius and scapula, right lateral malleolus, and both clavicles. Gross rickets and secondary hyperparathyroidism was shown radiographically (Fig. 1) and chemical analysis of plasma showed calcium 2.18 mmol/l (8.7 mg/100 ml), phosphate 1.02 mmol/l (3.1 mg/100 ml), alkaline phosphatase 1220 IU/l. Plasma urea was 2.2 mmol/l (13 mg/100 ml) and there was a generalized aminoaciduria but no reducing substances in the urine. There was no clinical suggestion of intestinal malabsorption.

She had had infantile spasms with hypsarrhythmia between the ages of 5 and 10 months but was not treated at that time. The diagnosis of tuberous sclerosis had been made at the age of 4 years when she presented with generalized seizures and mental retardation, from which time she had taken primidone, ethosuximide and sulthiame subsequently having been added. Her diet had been normal, though she had never liked milk, and she had not been deprived of exposure to sunlight.

Treatment was begun with calciferol 10 000 units daily, increasing after 3 months to 15 000 units daily, and supplemental calcium (Calcium Sandoz 30–45 ml daily). There was gradual radiographic and biochemical (Fig. 2) improvement, though the plasma calcium was still low after 6 months of treatment.

Case 2. A 13-year-old boy with mental retardation, temporal lobe epilepsy, adenoma sebaceum, cutaneous neurofibromata, a shagreen patch, and intracranial calcification presented with infantile spasms at the age of 3 months, when he was treated with ACTH and phenobarbitone. He took phenobarbitone continuously to the age 12 years, when primidone was substituted because of his aggressive behaviour, for which he was also given diazepam and later thioridazine. There was no clinical evidence of rickets, but investigation showed plasma calcium 2.55 mmol/l (10 mg/100 ml), phosphate 1.82 mmol/l (5.6 mg/100 ml), and alkaline phosphatase 640 IU/l; plasma 5-nucleotidase 5.5 IU/l. X-rays of pelvis, scapulae, wrists, and knees were normal. Treatment was started with calciferol 1000 units daily, and plasma alkaline phosphatase fell gradually to 317 IU/l over the next 3 months.

FIG. 1.—Case 1. X-ray of right wrist at time of presentation with rickets. There are also gross hyperparathyroid erosions, presumably secondary.
anticonvulsant associated rickets, one of whom suffered from tuberous sclerosis. They quoted Stößmann (1971) and a personal communication from Kruse (1972) as reporting tuberous sclerosis in 1 out of 4 and 2 out of 11 of their respective series of patients with rickets on anticonvulsant therapy. Dent et al. (1970) reported 4 cases of anticonvulsant drug osteomalacia, including one boy with intracranial calcification and an early history of infantile spasms who may have had tuberous sclerosis (A. Richens, personal communication, 1975). Of 5 patients studied by De Luca et al. (1972), one was shown at necropsy to have tuberous sclerosis, though the diagnosis had not been suspected during life (M. W. Partington, personal communication, 1976). Fischer, Fortune, and Gerritsen (1973) found high values of serum alkaline phosphatase in all of 7 patients with tuberous sclerosis. No details of treatment are given in their paper, but it seems likely that many of the children were taking long-term anticonvulsant therapy. In untreated children with tuberous sclerosis, Rundle, Fannin, and Bartlett (1967) reported low values of serum alkaline phosphatase.

It seems, therefore, that children with tuberous sclerosis may be particularly liable to develop rickets on anticonvulsant therapy. This liability most likely reflects the fact that many children with tuberous sclerosis need prolonged and intensive anticonvulsant therapy, though we are impressed that we have not seen this complication so frequently in other children who have had equally intensive and lengthy treatment. None of our patients had evidence of gastrointestinal or renal disease, but 2

Discussion
Borgstedt et al. (1972) described 2 children with

### TABLE
Details of 5 patients with tuberous sclerosis and rickets

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at start of anticonvulsant therapy (yr)</th>
<th>Age at diagnosis of rickets (yr)</th>
<th>Severity of rickets</th>
<th>Dose of calciferol (units/day)</th>
<th>Anticonvulsant treatment at time of rickets</th>
<th>Other anticonvulsant treatment given previously</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>14</td>
<td>++ +</td>
<td>15 000</td>
<td>Primidone, sulthiame, ethosuximide</td>
<td>Phenobarbitone, diazepam</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>13</td>
<td>↑ Alk phos only</td>
<td>1000</td>
<td>Primidone, thioridazine</td>
<td>Phenobarbitone</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>3</td>
<td>+ +</td>
<td>5000</td>
<td>Phenytinon, primidone, carbamazepine</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>5</td>
<td>+ +</td>
<td>3000</td>
<td>Phenytinon, primidone, carbamazepine</td>
<td>Phensuximide, desamphetamine, acetazolamide, sulthiame, carbamazepine</td>
</tr>
<tr>
<td>5</td>
<td>3 yrs</td>
<td>12</td>
<td>++</td>
<td>3000</td>
<td>Phenytinon, phensuximide</td>
<td></td>
</tr>
</tbody>
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Short reports

Motor nerve conduction velocity in spinal muscular atrophy of childhood

Spinal muscular atrophy is a hereditary disease characterized by degeneration and loss of motor neurones in the spinal cord and brain stem. Three clinical forms are recognized. The severe infantile form of the disease usually has an early onset, either in utero or within the first 2–3 months, and death usually occurs within the first 2 years from severe respiratory involvement. The intermediate form is characterized by normal motor development up to the age of about 6 months, with the infants usually achieving the ability to sit, but unable thereafter to take weight on their legs or to stand and walk. In the mild form the children have normal milestones in the first year of life and are able to walk but show evidence of muscle weakness. Not all cases of spinal muscular atrophy fall neatly into these three categories; many borderline cases are also encountered.

The motor nerve conduction velocity is generally considered to be normal in diseases of anterior horn cells, including spinal muscular atrophy (Munsat et al., 1969; Hausmanowa-Petrusewicz, 1970). However, Gamstorp (1967) found borderline or slow nerve conduction velocities in 6 infants with spinal muscular atrophy, all severely affected. Buchthal and Olsen (1970) noted ‘slightly decreased’ peroneal nerve conduction velocities in 3 of 9 patients with infantile spinal muscular atrophy.

In an extensive study of motor and sensory conduction velocities in Werdnig-Hoffmann disease, Raimbault and Laget (1972) found slow velocities for both motor and sensory fibres of ulnar and posterior tibial nerves in several of the patients. Hausmanowa-Petrusewicz et al. (1975) found motor nerve conduction velocities below normal in the ulnar, peroneal, and median nerve in 15, 7, and 3 cases of Werdnig-Hoffmann disease respectively.

This report describes the results of motor nerve conduction velocities in children with spinal muscular atrophy of different severity.

Materials and methods

This study comprises 29 children with spinal muscular atrophy in whom the diagnosis was subsequently confirmed by electromyography (EMG) and muscle biopsy. Their ages ranged from 3 months to 12 years. 12 were male and 17 female. For the purposes of this study they were placed into one of the following groups.

1. Severe (14 infants): this included all those infants with onset at birth or within 3–4 months of age, with severe paralysis and death usually within the first year.
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