Case 2

A 15-year-old boy had been ill for a week with malaise, fever, loss of appetite, and mild cervical adenopathy. A probable diagnosis of infectious hepatitis seemed confirmed with the onset of jaundice. He remained ill, however, and was thought to be pale. Investigations confirmed anaemia (haemoglobin 9.6 g/100 ml). The W.B.C. was 8,400/mm³ (neutrophils 2,900, lymphocytes 3,600, monocytes 450, and atypical lymphoid cells 1,450/mm³). Many spherocytes and polychromatic cells were present, and the reticulocyte count was 10.2%. The Paul-Bunnell test gave a titre of 160. Results of the direct antiglobulin test and test for cold agglutinins were negative. The degree of osmotic fragility was compatible with spherocytosis. Autohaemolysis at 24 hours was 3.8% without glucose, 1.8% with glucose, and 4.1% with adenosine triphosphate. Two brothers, the mother, and an aunt also showed increased fragility, reticulocytosis (5.1%, 4.8%, 8.1%, and 5.3% respectively), and scanty spherocytes in their peripheral blood. The patient recovered rapidly over the next 10 days.

Case 3

A 10-year-old girl presented with cervical adenopathy, sore throat, and pallor. Leukaemia had been considered until the onset of jaundice that morning. The peripheral blood showed haemoglobin 10 g/100 ml, and the W.B.C. was 4,600/mm³ (neutrophils 1,100, lymphocytes 3,200, and monocytes 300/mm³); rare atypical lymphoid cells were present. Only occasional spherocytes were seen but polychromatic cells were plentiful, and the reticulocyte count was 9%. The Paul-Bunnell test gave a titre of 80. Results of direct antiglobulin tests and tests for cold agglutinins were negative. The degree of osmotic fragility confirmed spherocytosis. Autohaemolysis at 24 hours was 6.1% without glucose, 5.3% with glucose, and 5.8% with adenosine triphosphate. Family studies showed pre-existing evidence; the father had had a splenectomy and a brother showed spherocytes in the peripheral blood.

The patient recovered without specific treatment.

Comment

It is generally accepted that congenital spherocytosis may be aggravated by infective episodes, leading to increased haemolysis or transitory hypoplasia.

In view of mounting evidence relating infectious mono-

nucleosis to E.B. virus infection and the increasing frequency with which infectious mononucleosis is being diagnosed the coincidence of infectious mononucleosis and congenital spherocytosis should become more widely recognized. Though there is a definite relation between agglutinability of red cells in hereditary spherocytosis and anti-i (Giblett and Crookston, 1964), and in some previous examples of haemolytic episodes in hereditary spherocytosis complicated by infectious mononucleosis anti-i has been found in the sera (Young *et al.*, 1951; Bean, 1957; DeNardo and Ray, 1963), anti-i was not detected in the present cases.

Aplastic episodes are well recognized in hereditary haemolytic disorders and may be induced experimentally by viral infection. Some degree of erythroid depression during an attack of infectious mononucleosis may thus allow recognition of previously inapparent congenital spherocytosis by reducing the compensatory power of the bone marrow. In all three cases described here a reticulocytosis was present, and it must therefore be assumed that any such impaired marrow function had occurred at a stage before clinical presentation.

Initially case 2 was thought to be suffering from infectious hepatitis, a well recognized diagnostic dilemma. Since infectious hepatitis itself may be complicated by more or less florid degrees of haemolysis this difficulty may be enhanced unless the possibility of coexistent disease is borne in mind. In two earlier cases sulphonamides had been ingested (Dameshek 1943; Gehlbach and Cooper, 1970), and an unusual reaction to drugs might, in those cases, have been a causal factor. Previous drug therapy had not been given in any of the three present cases.

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Myopathy associated with Anticonvulsant Osteomalacia

C. D. MARSDEN, E. H. REYNOLDS, V. PARSONS,
R. HARRIS, L. DUCHEN

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Myopathy has been described in association with all forms of osteomalacia except the sex-linked form of type 1 hypophosphatemia.

Institute of Psychiatry, London SE5 8AF

C. D. MARSDEN, M.Sc., M.R.C.P., Professor, University Department of Neurology
 E. H. REYNOLDS, M.D., M.R.C.P., Lecturer, University Department of Neurology
 L. DUCHEN, F.R.C.PATH., Reader, Department of Neuropathology

King's College Hospital, London SE5

V. PARSONS, D.M., F.R.C.P., Consultant Physician

Department of Clinical Neurophysiology, The Bethlem Royal and Maudsley Hospitals

R. HARRIS, M.D., D.C.H., Consultant

phataemic rickets (Smith and Stern, 1967, 1968). So far as we are aware myopathy in association with anticonvulsant osteomalacia, has not been reported previously, apart from a reference to proximal weakness in one of the four cases (Case 2) of anticonvulsant osteomalacia described by Dent *et al.* (1970).

Case Report

A 36-year-old Irish housewife was admitted to hospital for investigation in June 1972.

She had been mentally retarded since birth, and her full scale I.Q. (W.A.I.S.) was 68. Grand mal seizures began at the age of 11, since when she had been treated with varying doses of phenobarbitone and diphenylhydantoin. On admission she was taking phenobarbitone 200 mg daily, diphenylhydantoin 300 mg daily, sulthiame 600 mg daily, and amitriptyline 150 mg daily.

In 1964 she twice took an overdose of anticonvulsant tablets. During 1966 she first complained of back pain which was attributed to depression, and she improved after two courses of electroconvulsive therapy. From 1968 onwards she became progressively disabled by weakness and pain. The weakness was proximal in distribution, affecting legs more than arms. As a result she had increasing difficulty in rising from a bed or chair, in climbing stairs, and in lifting heavy objects or raising her arms to comb her hair. The pain was experienced in the back, left shoulder, and hip. By 1970 she was housebound and by the time of her admission

she was able to walk only a few yards with great difficulty and with the support of a stick. Throughout the previous four years she had attended eight other hospitals at each of which a diagnosis of hysteria or depression was made, and during this time she had received two further courses of electroconvulsive therapy and numerous courses of antidepressant drugs, none of which had affected the progression of her symptoms. Direct questioning revealed a probably poor diet, but details were difficult to establish.

On examination facial, jaw, and neck strength were normal. There was severe symmetrical proximal weakness of her arms and legs, the latter being most affected, and severe weakness of trunk muscles. She was unable to rise from the lying position or from a chair without help. Distal strength was normal. There was no wasting or fasciculation, tendon reflexes were normal, and plantar responses were flexor. Sensation was normal. There was a pronounced dorsal kyphosis with local tenderness over the thoracic and lumbar spine, and pain and limitation of movement of the left shoulder and hip.

Investigations showed no evidence of epilepsy. The skull x-ray findings were normal. An E.E.G. showed generalized slow-wave activity but no focal or paroxysmal features. C.S.F. examination showed nothing abnormal. Serum phenobarbitone was 11.6 $\mu\text{g/ml}$, serum diphenylhydantoin 7.2 $\mu\text{g/ml}$, and serum creatinephosphokinase 33 IU/l. (normal). Electromyography showed small polyphasic units on volition in left vastus medialis, right deltoid, wrist extensors, and abductor pollicis brevis. Maximal motor conduction velocity in the right median nerve was 61.1 m/sec, and a sensory action potential of 11 μV was recorded over the right median nerve at the wrist after stimulation of the index finger, with a latency of 2.2 msec. The conclusion was that there was evidence of a widespread myopathic process with normal motor and sensory conduction. A muscle biopsy specimen was taken from the left deltoid. On light microscopy muscle fibres showed a wide variation in size and many very small fibres were scattered among those of larger diameter. There was no fascicular distribution of atrophied fibres. Occasional degenerating muscle fibres and many with centrally placed nuclei were present and there were many long rows of nuclei. Silver impregnation showed normal axons in the intramuscular nerve bundles and the preterminal axons also looked normal. At most of the end plates axonal terminals were normal in appearance, but some were thickened and tortuous while at a few other endplates there were thin beaded terminals.

Electron microscopy showed abnormal muscle fibres in each block sectioned. The most severe abnormality was a degeneration of part of the muscle fibre with complete disappearance of myofilaments leaving only granular amorphous material, vacuoles, and occasional dense nuclei. No inflammatory or phagocytic cells were seen in these necrotic muscle fibres. Usually both sarcolemmal and basement membranes were intact but in some places only the basement membrane remained intact. In some fibres there was a fairly abrupt edge to the structureless necrotic part of the fibre, but the myofilaments in the remaining part of these fibres were severely disorganized and lacked any arrangement into sarcomeres. Many other muscle fibres contained regions in which filaments lay in disarray, but a striking feature was the presence of dense wide masses of Z-line material. Such regions lay both at the periphery beneath the sarcolemma and in the central part of muscle fibres. In some areas the organization of filaments was apparently normal but patches of Z-line were widened and dense.

A skeletal x-ray survey showed evidence of gross osteomalacia, with pseudofractures of the left scapula, iliac bones, second right

and third left metacarpals, and pathological fractures of several ribs. In the hands there was also subperiosteal bone resorption, suggestive of secondary hyperparathyroidism. Serum calcium was 8.0 mg/100 ml, serum phosphate 2.0 mg/100 ml, serum alkaline phosphatase 233 IU/l., 24-hour urinary calcium excretion 69 mg, 24-hour urinary hydroxyproline excretion 61.1 mg (high), and serum 25-hydroxycholecalciferol (Dr. T. Stamp) 3 ng/ml (very low). A bone biopsy specimen from the right iliac crest showed evidence of severe osteomalacia.

Her haemoglobin was 14.6 g/100 ml; M.C.V. 112 μm^3 (blood film confirmed severe macrocytosis); E.S.R. 43 mm in 1 hour (Westergren); serum folate 1.3 ng/ml (subnormal), red-cell folate 163 ng/ml (subnormal); serum vitamin B₁₂ 155 $\mu\text{g/ml}$; Schilling test of Vitamin B₁₂ absorption, normal; blood urea and electrolytes, normal; results of liver function tests, normal; protein electrophoresis showed a slight increase in α_2 -globulin; protein bound iodine, normal; xylose absorption, faecal fat excretion, barium-meal appearances, and follow-through were all normal. Urine contained no protein, cells, or sugar.

She was treated with vitamin D, calciferol 1.2 mg/daily, and folic acid 10 mg daily. Her anticonvulsant medication was continued unchanged. At latest follow-up after six months of treatment, pain had completely disappeared and there had been a remarkable improvement in muscle strength. She could use her arms normally, was able to get out of a chair, and could walk several hundred yards without the aid of her stick. She was then taking charge of domestic activities and getting out of the house to help with shopping.

Comment

This patient had clinical, biochemical, radiological, and bone biopsy evidence of severe osteomalacia. In the absence of evidence of gastrointestinal or renal disease it is concluded that her osteomalacia was due to prolonged anticonvulsant therapy, possibly aggravated by dietary factors.

The features of her myopathy are similar to those previously described in association with other forms of osteomalacia (Smith and Stern, 1967, 1968). Some of these features deserve emphasis as they partly account for the long delay in establishing the diagnosis. These include the absence of wasting, the normal reflexes, and normal levels of creatine phosphokinase. However, the characteristic distribution of the weakness confined to the trunk and limb-girdle muscles is typical of a myopathic process, which was confirmed in this patient by electromyography and muscle biopsy. With increasing awareness of osteomalacia as a complication of anticonvulsant therapy we suspect that further examples of this myopathy will come to light.

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