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 polychromatophilic 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 polychromatophilic 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-

Myopathy associated with Anticonvulsant Osteomalacia

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

phaeic 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 pheno-

References

tology, 7, 141.
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 re-
vealed 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 pro-
nounced 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 μg/ml, serum diphenylhydantoin 7.2 μg/ml, and
serum creatinephosphokinase 33 IU/1. (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
atrophy 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 myo-
fibres 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 base-
ment 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-hydroxycalciferol (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 μm³
(blood film confirmed severe macrocytosis); E.S.R. 43
mm in 1 hour (Westergren); serum folate 1-3 mg/ml (subnormal), red-
cell folate 163 ng/ml (subnormal); serum vitamin B₁₂ 155 μg/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 α₂-globulin; protein
binding was normal; xylese 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 previ-
ously described in association with other forms of osteo-
malacia (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 wast-
ing, the normal reflexes, and normal levels of creatine phospho-
kinease. 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 in-
creasing awareness of osteomalacia as a complication of anti-
convulsant therapy we suspect that further examples of this
myopathy will come to light.

References

British Medical Journal, 4, 69.