Progress

No active measures were advised and the child was observed in the clinic. The episodes of dislocation described so clearly by his mother have decreased in frequency as far as the left hip is concerned and, during the last 4 months, only one episode has occurred. The cause of the improvement is not explained, other than supposing that a change in sleeping posture has been adopted by the child. The right patella dislocates regularly with every flexion of the knee, but no surgery is contemplated yet. The right hip and left knee remain lax but not unstable.

We have examined the sibs; the eldest boy (16 years) is normal; the second boy (14 years) and the third boy (7 years) have hyperextensible metacarpophalangeal joints, but all other joints are normal: their skins are soft in texture. The youngest child (a girl aged 3) and her parents are normal.

Comment

It is unlikely that this child has congenital dislocation of the hips, since no abnormality was detected in the neonatal period. Children with Down's syndrome often appear loose jointed because of the associated muscle hypotonia, but generalized joint hypermobility is also described in Down's syndrome (Penrose and Smith, 1966). Our patient fulfils the criteria suggested by Carter and Wilkinson (1964), and can be regarded as a mild case of arthrochhalasis multiplex congenita, as described by Hass and Hass (1958). The gross joint laxity may, in this case, be the result of the combination of two predisposing conditions: the familial tendency as evidenced in his brothers, and the hypermobility associated with Down's syndrome. The late onset of recurrent dislocation of the hip and apparent spontaneous regression at the age of 8½ years, presumably due to changes in his sleeping posture, are also of interest. The arthrographic studies show the dynamics produced across the hip joints and the mechanics involved in producing the dislocation.

Summary

Clinical and familial details are given of a case of severe joint laxity where arthrographic studies of both hip joints were carried out to show the mechanics involved in producing the dislocation.

The various conditions presenting with generalized hypermobility of joints are briefly reviewed. It is concluded that this can be regarded as another case of 'arthrochhalasis multiplex congenita'.

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Chronic lactic acidosis in association with myopathy

In 1962 Luft and his colleagues described a patient with a hypermetabolic state and a myopathy associated with partial uncoupling of oxidative phosphorylation within structurally abnormal muscle mitochondria. Other patients with myopathy and mitochondrial abnormalities have since been reported, but in only one was a raised plasma level of lactate noted (van Wijngaarden *et al.*, 1967).

The following report describes a girl with a marked limb girdle myopathy, raised plasma levels of lactate, pyruvate, and alanine, and bizarre mitochondrial changes in the muscles.

Case report

The patient, a girl, is the second child of unrelated parents. Pregnancy, birth, and early motor development were normal. At 4½ years of age she developed increasing lassitude, weakness, and episodic vomiting.

On examination, aged 6 years, her height was 102 cm and weight 14 kg (both below the 3rd centile); there was marked weakness in the muscles of the trunk, shoulder, and pelvic girdles. She could not lift her arms above her head, could only climb upstairs on all fours, and could walk only 30 to 50 m without tiring. There was also slight weakness in the small muscles of the hands, and the muscles tired readily. No other neurological or other abnormalities could be detected. An edrophonium test for myasthenia was negative.

Plasma creatine phosphokinase level was 9.6 µmol/ml

per hr (normal 0.5–2.0 $\mu\text{mol/ml}$ per hr). Electromyogram (R.deltoid) showed no fibrillation potentials at rest; on volition, many of the motor unit potentials obtained were of disintegrated outline and short duration, findings characteristic of a myopathic state. Plasma electrolytes on admission showed a widened 'anion gap' ($\text{Na}^+ - (\text{Cl}^- + \text{CO}_2)$), suggesting that the acidosis was due to an organic acid, and this was confirmed by a plasma lactate level of 7.2 mEq/l. (nonfasting normal <1.0 mEq/l.). Alanine levels were raised in both plasma (12 mg/100 ml) and urine ('marked excess'). Other plasma and urine amino acids were normal. Plasma levels of pyruvate and lactate fluctuated during the period of observation but remained consistently above the normal range; this fluctuation was not related to changes in the clinical condition. The basal metabolic rate and respiratory quotient were normal.

Neither a 2-week course of oral thiamine (600 mg daily) nor alkali therapy led to improvement in muscle function or in plasma lactate and pyruvate levels.

Over the past 3 years her clinical condition has gradually ameliorated, though there is persisting evidence of a mild proximal myopathy. Plasma lactate remains high at 3.2 mEq/l., and plasma creatine phosphokinase is persistently raised (last value 5.4 $\mu\text{mol/ml}$ per hr). She can now, however, walk 1 km on the flat without tiring.

Histology, histochemistry, and electron microscopy. Muscle biopsy was taken from the rectus

abdominis. Histology (Dr. C. L. Berry) showed extensive destruction of muscle with fragmentation and granulation of the myofibrils; many swollen histiocytes were present in the fragmenting fibres, and there was no evidence of regeneration. Gomori's trichrome method showed increased red staining in the degenerating fibres, which also stained with Sudan Black and PAS, the intensity apparently being related to the degree of degeneration. Overall glycogen content was normal.

Dehydrogenase reactions all showed intense staining of affected fibres. The degenerating fibres showed a strong 'ATPase' reaction which could not be reversed by EDTA pretreatment. This method showed a normal distribution of Type I (red) and Type II (white) fibres; both types of fibre appeared equally affected by the myopathy.

Mildly affected fibres showed occasional collections of mitochondria in degenerate I bands; in others, the fibrils were irregularly spaced. Occasional lipid droplets were also present. In severely affected muscle the fibres appeared to have been replaced by a few vacuoles (nonlipid-containing) and by numerous bizarre pleomorphic mitochondria. In some areas, grossly enlarged mitochondria were found (up to 4 μm in length and 1 μm in width). These were filled with closely packed tortuous cristae, among which were found occasional large osmophilic bodies (Fig. 1).

Family study. The results of random estimations of plasma lactate, pyruvate, and creatine phosphokinase on

FIG. 1.—Electron photomicrographs showing bizarre pleomorphic mitochondria. Stained with uranyl acetate and lead citrate. Scale mark 1 μm . (a) Annular shaped sections of two mitochondria. (b) Tightly packed cristae and dense inclusions are features of many mitochondria.

FIG. 2.—Plasma creatine phosphokinase estimations in first-degree relatives of the patient showing the autosomal dominant pattern of inheritance.

all first-degree relatives are shown in Fig. 2. Apart from the patient's mother, no other member of the family has raised plasma lactate or pyruvate levels, though several have raised plasma creatine phosphokinase.

The patient's maternal uncle (II.2) is small, and was 'weak' in childhood. His 17-year old daughter (III.2) is also short, but is symptom free.

The creatine phosphokinase levels suggest the myopathy is inherited as an autosomal dominant, with variable expressivity.

Discussion

Apart from tissue anoxia (Litwin *et al.*, 1959), lactic acidosis has also been described in severely ill patients who are not hypoxic. This latter 'idiopathic' lactic acidosis was thought to be a grave prognostic sign, usually followed by death within hours (Huckabee, 1961). More recently, however, some patients with Leigh's encephalopathy (Clayton, Dobbs, and Patrick, 1967), with cerebellar ataxia (Lonsdale *et al.*, 1969), and with leukaemia (Field, *et al.*, 1966) have been shown to have 'chronic' lactic acidosis, which, in these patients, clearly does not have such a grave immediate prognosis. Our patient has actually improved over 3 years' observation, despite her lactic acidosis.

Raised plasma pyruvate and alanine are consistently found in patients with lactic acidosis, the 3 compounds being interconvertible through the actions of lactate dehydrogenase and pyruvate transaminase. Adults with lactic acidosis have normal or increased peripheral release of alanine and impaired hepatic disposal, and high levels of lactate and pyruvate perfusing rat liver have been shown to impair *in vitro* uptake and disposal of alanine (Marliss *et al.*, 1972).

The disorganized cristae and gross pleomorphism suggest that the mitochondria are functionally

abnormal, and the histochemical changes can best be explained in this way. Increased numbers of mitochondria would account for the increased red staining with Gomori's trichrome method, and for the heavy staining with the dehydrogenase techniques. The apparent hyperactivity of Krebs' cycle enzymes may reflect either this, or an increased permeability of damaged mitochondria to histochemical substrates.

It is hoped that this brief report will stimulate the search for more generalized metabolic disorders in other patients with proximal myopathies.

Summary

In a 7-year-old girl proximal limb girdle myopathy with lactic acidosis, hyperpyruvicemia, and hyperalaninaemia was associated with bizarre mitochondrial changes in the muscle fibres on electron microscopy. The mitochondria were pleomorphic with numerous disorganized cristae and their number was increased. Family studies suggested an autosomal dominant inheritance of variable expressivity. Some spontaneous improvement has occurred over the 3 years she has been under observation.

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