Infection due to *Pasteurella pseudotuberculosis*

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P P, boy, aged 3½

History: Noted to have a systolic murmur at birth, probably due to a ventricular septal defect, for which he was being followed up. Never any symptoms of heart disease. Normal progress.

25.10.66: Liver impalpable. 22.11.66: Liver and spleen enlarged 3 fingerbreadths below costal margin. Admitted for investigation and gradually developed the picture of intestinal obstruction. Laparotomy 13.12.66 revealed an appendix abscess which was drained; satisfactory recovery.

Iliac crest marrow biopsy (16.12.66) showed normal marrow, but two small groups of acid-fast bacilli were seen. Tuberculin testing negative. 5.1.67: Agglutination reactions for *Pasteurella pseudotuberculosis* Type 4 were positive 1/800 for the 0 antigen and 1/1,600 for the H antigen; a week later they were 1/400 and 1/1,600 respectively.

Discussion

The genus pasteurella contains *P. septica* (= *multocida*), which causes hæmorrhagic septicæmia in a variety of wild animals, *P. pestis*, which causes plague, and *P. pseudotuberculosis*. The organism of tularæmia is sometimes included in the genus. *P. pseudotuberculosis* was described by Malassez & Vignal in 1883 as causing a disease in guinea-pigs characterized by nodules with a histology similar to tuberculosis. It is a small, ovoid, Gram-negative bacillus with slight acid-fast properties. It was found later to be a cause of endemic disease in a wide variety of wild animals throughout Europe and America.

Human infections with this organism appear to take two forms. There are about 20 reported cases of a severe typhoid-like illness with high fever, purpura and enlargement of liver and spleen, in which *P. pseudotuberculosis* has been recovered from blood or tissues. In 1953 Knapp, in Tübingen, recovered the organism from cases in which appendicitis had been suspected, but only enlarged mesenteric glands found at operation (Knapp 1958).

Diagnostic features of mesenteric adenitis due to pseudotuberculosis infection are: (1) A high titre of agglutinating antibodies to the organism (the figure depending upon the particular technique) which remains raised for about three months. (2) A characteristic tuberculoid histology in mesenteric glands (but not usually in the lymphatic tissue of the appendix). (3) Recovery of the organism from blood or glands, achieved in only a minority of cases.

Surveys have shown this to be a cause of a proportion of cases of mesenteric adenitis in Europe, Britain, Canada and New Zealand (Hnatko & Rodin 1963, Randall & Mair 1962).

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A Syndrome of Benign Congenital Hypotonia, Gross Obesity, Delayed Intellectual Development, Retarded Bone Age, and Unusual Facies

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Two children, followed from the neonatal period, have shown a remarkably similar pattern of disease.

Case 1 P N, boy, born 27.2.62

During pregnancy fœtal movements were frequently absent for up to three days. He was born at home, three weeks prematurely, on a very cold night. Birth weight 2·49 kg. Admitted to hospital at 2½ hours with neonatal cold injury (rectal temperature 93°F) and marked generalized hypotonia and immobility. Unable to suck or swallow. Tendon jerks and Moro and grasp reflexes absent. He had an unusal facies (Fig 1) and a dolichocephalic head. Penis small, scrotum rudimentary, and testes undescended.

At 2 weeks he was still grossly hypotonic, with severe head lag, but there were spontaneous movements of limbs. A diagnosis of benign congenital hypotonia was made, on the basis of hypotonia disproportionate to weakness. By 5 weeks spontaneous movements of the limbs improved, and he was able to suck, but still needed tube feeding. He first smiled at 9 weeks, and at that time had some head control in ventral suspension. There was subsequently a gradual improvement in tone and motor control. He sat with support at 8½ months, and unsupported at 11 months. He stood with support at 15 months, started to walk at 2 years, and walked well by 26 months. He was still hypotonic, but the power was good. The knee-jerks appeared at 13 weeks, and all tendon reflexes were present by 8½ months.

At 17 months, during a respiratory infection, he had two convulsions lasting less than five minutes each. Phenobarbitone was prescribed for three months. He had three further short convulsions at 2 years 11 months.

From birth to about 30 weeks his weight remained below the 10th percentile, but climbed at a normal rate. It then gradually rose to the 80th

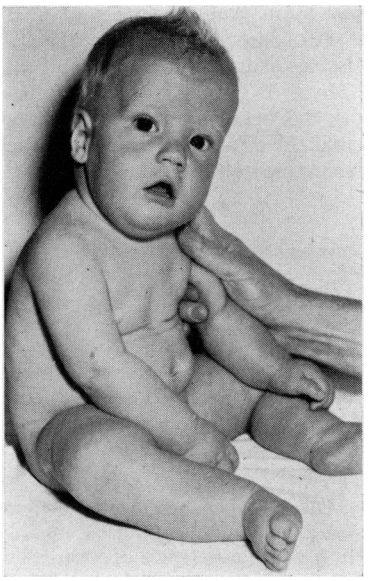

Fig 1 **Case 1** *Aged 8 months, showing typical facies and inability to sit unsupported*

percentile by 1 year and remained at that level till the age of 3, after which it started to rise precipitously, and is now, at 42·6 kg, more than twice the 90th percentile for his age (Fig 2). His height (107 cm), in contrast, is just below the 50th percentile. His bone age at 3 weeks was commensurate with a 36 week fœtus, and at present (5years) is at a 2·2 year level.

His early intellectual progress seemed reasonable, and the slight delay was disproportionate to the gross hypotonia. However, his subsequent progress has been very slow, and his present attainments are less than a 3-year-old level in most spheres.

His mother is overweight (77 kg) but of normal stature, father is of average weight, and two sibs are normal.

Special investigations: Serum creatine phosphokinase and aldolase normal; muscle biopsy (rectus femoris) at 4 months histologically and histochemically normal; 17-ketosteroids and 17-hydroxycorticosteroid excretion in urine and response to ACTH and metyrapone, normal; pituitary gonadotrophins markedly elevated (547 m.u.; 64·8 i.u. per day; urine volume 290 ml); protein bound iodine 6·2 μg/100 ml; glucose tolerance curve normal; chromosome karyotype normal.

Case 2 K D, girl, born 22.8.62

Cæsarean section at 36 weeks, following diagnosis of mild diabetes in mother during pregnancy. Birth weight 3·43 kg. Slow to cry at birth and very hypotonic. No hypoglycæmia. Unable to suck and needed tube feeding. The head was dolichocephalic and the facies strikingly reminiscent of Case 1.

At 6 weeks she still needed tube feeding and still had generalized hypotonia. Marked head lag, but good spontaneous movements of limbs. Knee and ankle jerks, present; other tendon jerks absent. A diagnosis of benign congenital hypotonia was made.

By 10 weeks she was sucking normally, started smiling and took an interest in her surroundings. At 16 weeks she could raise her head in the prone position. There was a gradual improvement and by 9 months she was sitting with support, and rolling from supine to prone. She sat unsupported at 1 year, stood with support and cruised at 19 months, stood with one hand held at 2 years and walked with hands held at 2½ years. She did not walk without support until 3½. At 6 months she had several short episodes of unconsciousness suggestive of convulsions, but these did not recur.

Up to 2 years her weight remained at about the 50th percentile but then rose precipitously and her present weight of 34·5 kg is almost double the 90th percentile (Fig 2). Her height of 99 cm, in contrast, is at the 10th percentile, and her bone age is at a 2-year level.

Her initial intellectual development seemed satisfactory. By 15 months she had a good vocabulary of single words and good manipulative skills. There has, however, been a gradual fall-off and although she now speaks in full sentences, her comprehension and also manipulative skills are retarded.

The mother is also obese (over 90 kg), but of

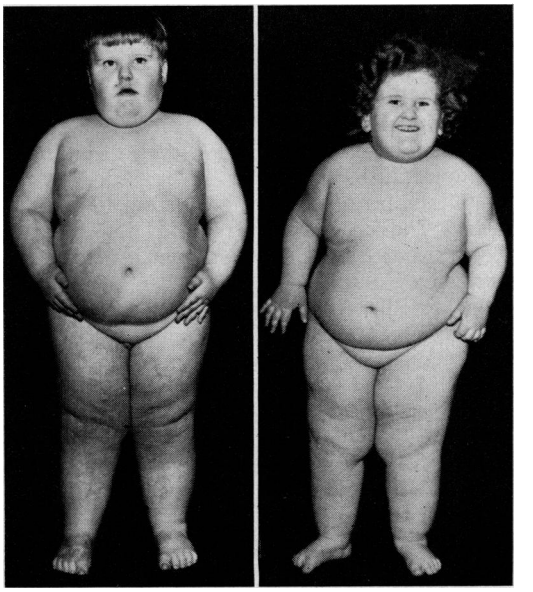

Fig 2 **Cases 1 and 2** *Aged 5 and 4½ years respectively*

normal height (168 cm); the father is of average weight. Two sibs are normal.

Special investigations: Serum creatine phosphokinase and aldolase normal; muscle biopsy (rectus femoris) at 7 weeks histologically and histochemically normal; 17-ketosteroid and 17-hydroxycorticosteroid excretion normal, with a normal response to ACTH and metyrapone; pituitary gonadotrophins normal (none detected); serum protein-bound iodine 6·1 µg/100 ml; glucose tolerance curve normal; chromosome karyotype shows abnormal No. 16, also present in mother, and probably a marker chromosome.

Discussion

These children have in common the following features: gross hypotonia at birth with gradual improvement; feeding difficulties in the neonatal period; dolichocephalic head and unusual facies with a triangular mouth; intellectual impairment, more apparent later; dramatic development of obesity after improvement in motor function; relatively retarded height; delayed bone age. In addition, the testes were undescended in the boy, and he had a number of grand mal convulsions. The girl possibly also had convulsions.

The picture is similar to the syndrome described by Prader *et al.* (1956) and Prader & Willi (1963). They noted, in addition, that there was later a diabetic tendency.

Similar cases have also been described by Dunn *et al.* (1961), Laurance (1961), Zellweger *et al.* (1962), Evans (1964), and Forssman & Hagberg (1964). The majority have been males.

It is difficult to explain this unusual combination of features. There has been no record of familial incidence and chromosome studies have been normal, with isolated exceptions (Dunn *et al.* 1961, Zellweger *et al.* 1962).

Evans (1964) suggested an insulin antagonist to explain the development of diabetes. This awaits further study. Apart from high levels of pituitary gonadotrophins, also observed by Prader *et al.* (1956), studies of endocrine function have been normal. The recognition of retarded bone age at 3 weeks in our Case 1, suggests that it may be an early feature of the disease.

The development of obesity after the improvement in muscle function is an unusual sequence. It suggests that the hypotonia and obesity are inversely related to each other through a common metabolic abnormality.

It should be possible to recognize this syndrome at birth from the features mentioned. It is probably quite common – I have seen 6 other typical cases (4 females, 2 male), and a number of possible ones. Since the hypotonia and subsequent obesity are the two most consistent features of the syndrome, I would suggest it be called the hypotonia-obesity syndrome (Prader-Willi).

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Dr H G Dunn (*Vancouver, Canada*) agreed that these two patients were examples of the Prader-Labhart-Willi syndrome. In his own experience of 9 cases he had also noted that the ultimate intellectual status at school age tended to be lower (IQ about 40 to 60) than had been anticipated at 2 to 3 years. Dr J M Martin, of the Hospital for Sick Children in Toronto, had examined the plasma of 6 of Dr Dunn's patients for synalbumin insulin antagonism, and had only found significant amounts of antagonist in one of them. The boy with an extra small chromosome reported earlier (Dunn, Ford, Auersperg & Miller 1961, *Pediatrics* **28**, 578) was now known to have an XYY sex chromosome complement; so far he showed no notable clinical differences from the other patients with the syndrome and was neither taller nor more aggressive. The mean age of the parents at the birth of the child was somewhat high in Dr Dunn's experience but not in some other series of cases.

Dr B M Laurance (*Derby*) agreed that Dr Dubowitz's patients bore a striking facial resemblance to those described by Prader & Willi, as well as to those of Dr Philip Evans and himself. The facial appearance was typical, especially in side view when the high head above the ears and retroussé nose was characteristic. In connexion with Dr Dunn's comments on paternal age, this was not significantly high in Dr Laurance's patients.

To Dr Dubowitz's clinical description, Dr Laurance added that scoliosis had been present in several of his own patients as well as in those patients of colleagues whom he had seen with this syndrome. Radiography did not show any structural cause for the scoliosis; as muscle biopsy and enzyme studies in his own patients, and apparently in those of Dr Dubowitz, had not revealed any muscle disorder, the ætiology of the scoliosis remained unknown.

The following case was also shown:

Precocious Puberty Secondary to Malignant Teratoma

Mr Austin Wheatley and Dr D Morris