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Recurrent Haemophilus Septicaemia and Immunoglobulin Deficiency

Infection with *Haemophilus influenzae* type b is often subclinical but may give rise to septicemic illnesses (Farrand, 1969). One infection appears to give long-lasting immunity (Fothergill and Wright, 1933). Hypo- γ -globulinaemia or splenectomy can predispose to a single attack of haemophilus meningitis, or to repeated respiratory infections due to non-capsulated organisms. Recurrent pneumococcal septicaemia has often been described in immune-deficiency syndromes, but in a survey of the published papers no report of a second episode of haemophilus septicaemia was found (Good *et al.*, 1960; Eraklis *et al.*, 1967).

Case History

This 10-month-old boy was found in a collapsed state, with clinical signs of meningitis. CSF contained 4800 polymorphonuclear cells per cu. mm., with a protein of 256 mg./100 ml. and glucose of 25 mg./100 ml.

The stained film showed Gram-negative bacilli, and on culture *H. influenzae* type b was isolated in large numbers. Blood cultures also yielded *H. influenzae* type b. WBC 15,600 per cu. mm. (53% neutrophils, 40% lymphocytes, 7% monocytes). The patient was treated with ampicillin and responded satisfactorily. He was discharged home fully recovered after two weeks, and ampicillin was withdrawn after one further week.

The boy had been in good health before his attack of meningitis, and had not previously suffered any infection of note. He remained very well for four months, until when aged 14 months he developed otitis media. This relapsed after a 5-day course of penicillin and was treated with ampicillin for 7 days with full recovery. No bacteriology was undertaken, but as *H. influenzae* type b is a common cause of otitis media in early childhood, and characteristically shows resistance to penicillin and response to ampicillin, it seems very likely that this episode of infection also was caused by *H. influenzae*.

One month later, aged 15 months, the boy became febrile again, and was admitted to hospital with a temperature of 40 °C. He was reluctant to use the right arm, and there was some local tenderness over the inner margin of the right humerus but no sign of local inflammation and no definite abnormality on x-ray examination. CSF normal; WBC 16,900 (84% neutrophils); ESR 20 mm./hr. Blood cultures were taken. No precise diagnosis was possible at this stage, and the possibility of an early focus of osteomyelitis in the humerus was noted. Large doses of intramuscular benzyl-penicillin were given, and after 24 hours the temperature returned to normal.

He was allowed to continue with oral penicillin at home, but after three days was readmitted with an inflammatory swelling over the distal end of the right humerus. ESR had risen to 73 mm. per hour, and further blood cultures were taken. Osteomyelitis of the right humerus was diagnosed, and treatment started with ampicillin and lincomycin.

H. influenzae type b was isolated from the initial blood

TABLE
Immunoglobulin Levels and H. influenzae Type b Capsular Antibody Titres

	Age	IgA (mg./100 ml.)	IgG (mg./100 ml.)	IgM (mg./100 ml.)	<i>Haemophilus influenzae</i> type b Haemagglutination Titre
Case: 1st specimen (day 12 of osteomyelitis)	15 mth.	Undetectable (72 $\pm$ 35)	130 (792 $\pm$ 216)	220 (47 $\pm$ 18)	Nil
Case: 2nd specimen (day 23 of osteomyelitis)	15 mth.	Undetectable (72 $\pm$ 35)	130 (792 $\pm$ 216)	83 (47 $\pm$ 18)	Nil
Father	Adult	300 (288 $\pm$ 121)	1500 (1200 $\pm$ 300)	83 (80 $\pm$ 29)	Nil
Mother	Adult	110 (288 $\pm$ 121)	1000 (1200 $\pm$ 300)	220 (80 $\pm$ 29)	128
Brother	7 yr.	140 (178 $\pm$ 58)	1000 (960 $\pm$ 264)	135 (53 $\pm$ 20)	64
Sister	5 yr.	30 (135 $\pm$ 40)	500 (960 $\pm$ 240)	83 (46 $\pm$ 15)	4
Sister	3 yr.	50 (136 $\pm$ 40)	500 (960 $\pm$ 240)	140 (46 $\pm$ 15)	16

Normal levels of immunoglobulin are shown in parentheses (Stichm and Fudenberg, 1966).

culture, and from that taken four days later on re-admission.

Response to ampicillin was prompt, and there was full recovery within two weeks. He was then discharged home to continue with oral ampicillin for three months.

Epidemiology

The family consisted of 3 children in addition to the patient, girls of 3 and 5 years, and a boy aged 7. The elder girl was achondroplastic and hydrocephalic, but had not been hospitalized during the previous 2 years. The mother suffered an attack of sinusitis in the month before the patient developed meningitis, but from then until after the second episode no other member of the family had any infection of note.

At the time of the second illness, nose and throat swabs were taken from all members of the family, and *H. influenzae* type b was isolated from the throats of the 2 girls. Additional information on carriage of the organism was obtained by examining blood samples, taken at the same time, for antibodies to type b polysaccharide. The haemagglutination method of Turk and Green (1964) was used, and the titres obtained are shown in the Table. The abnormally high titres of the mother and elder boy indicate that they too had been carriers. The findings suggest that the type b haemophilus was carried first by the mother, perhaps from the time of her sinusitis, and then by the elder brother before being transmitted to the girls.

In an attempt to clear the family of nasopharyngeal carriage of *H. influenzae* type b, framycetin was sprayed into the nose and throat of both girls, thrice daily for two weeks. During this period, the elder boy underwent tonsillectomy. Two weeks later the swabs were repeated, and *H. influenzae* type b was isolated from the throat of the younger girl, and the nose of the elder boy.

Immunology

Serum levels of IgG, IgM, and IgA were determined by a radial immunodiffusion method using commercially available materials (Immunoplates, Hyland Laboratories, Los Angeles, California). The results are shown in the Table.

No trace of IgA was detectable in samples of the patient's serum, though the method was readily sensitive to 5 mg./100 ml. IgG was also very low. A raised IgM was shown in the acute phase sample, but no specific antibody to type b haemophilus was demonstrated.

The female members of the family also showed low levels of IgA and IgG.

Discussion

The second episode of septicaemia was regarded as a separate reinfection and not a relapse because of the long period of good health after the meningitis. This contrasts with the immediate relapses reported after unsuccessful treatment (Young, Haddow, and Klein, 1968). The absence of antibodies to haemophilus seemed to support this.

Families of patients with haemophilus meningitis tend to be large and to enjoy high standards of care and hygiene (Turk, 1968). Both features were apparent in this family—there were four young children and the father is a professional man. Cases of haemophilus meningitis are thought to represent the end-result of a sequence of bacterial passages from one member of the family to another before eventually the youngest develops septicaemia (Turk and May, 1967).

A high concentration of nasopharyngeal carriers of haemophilus in the home is not associated with significant disease unless septicaemic invasion occurs, and no previous attempts to clear symptomless carriers appear to have been reported. Eradication of *H. influenzae* type b from the nasopharynx seems an intractable problem: ampicillin has failed to eliminate the organism from a patient treated for epiglottitis (Andrew, Tandon, and Turk, 1968), and our experience does not recommend topical framycetin or tonsillectomy.

The finding of a deficiency of IgA and IgG, with a reciprocal increase in IgM, is in contrast to the suggestion of Hobbs, Milner, and Watt (1967) that it is IgM deficiency which predisposes to meningococcal septicaemia.

H. influenzae resembles the pneumococcus in that virulent strains possess a polysaccharide capsule, and it is thought that the immunological response to these polysaccharides rests entirely on the immunoglobulin system, being independent of thymus-dependent cell-mediated immunity (Roitt *et al.*, 1969). However, the pneumococcus differs from *H. influenzae* in that many of its eighty or so capsular types may be virulent, whereas only one type of haemophilus causes septicaemia. It is this difference which may account for the relative frequency of recurrent pneumococcal septicaemia and the absence of previous reports of recurrent haemophilus septicaemia.

Effective immunity to a second challenge with type b haemophilus appears to develop even when no antibodies are detectable. Most patients with meningitis are treated too promptly for any antibody response to occur, and are then returned to the high concentration of *H. influenzae* type b in their family. In such a situation it is remarkable that reinfection does not occur regularly. The isolated absence of IgA is not always associated with symptoms, but Scuro *et al.* (1969) believe that IgA deficiency can cause disease, especially when associated with a partial deficit of IgG. This case indicates that the presence of IgA and IgG may be important in preventing reinfection and septicaemia due to *H. influenzae* type b.

Summary

A 15-month-old boy developed osteomyelitis five months after complete recovery from meningitis. *Haemophilus influenzae* type b was isolated from the blood during both episodes. The probable source of reinfection was persistent carriage of the organism in the family. Immunological studies revealed a deficiency of IgA and IgG in the patient's serum.

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Congenital Tuberculosis

The birth of a baby already infected with tubercle bacilli either during pregnancy or at the time of delivery is a rarity. Beitzke (1935) suggested the following criteria for a diagnosis of congenital tuberculosis; the tuberculous nature of the lesions in the infant must be proven; the lesions must be present at, or within a few days of birth; in cases

where tuberculosis is diagnosed after the first weeks of life, a primary complex must be found in the liver, or extrauterine infection must be excluded, the infant being separated immediately after birth from the mother or from any other possible source of infection. Applying Beitzke's criteria, Corner and Brown (1955) found 134 published cases; since then, occasional reports have appeared.

In spite of effective chemotherapy, congenital tuberculosis has a high mortality rate and only 6 cases have been reported with survival (Miller, Seal, and Taylor, 1963). This is due partly to the gravity of the condition, and partly to delay in diagnosis.

We report a case of congenital tuberculosis diagnosed by liver biopsy, successfully treated, and surviving apparently without sequelae.

Case Report

This female baby was the first child in the family, born with normal delivery after an uneventful pregnancy. Though born at term, her birthweight was only 2300 g. She was well until 40 days old when she suddenly developed fever and abdominal distension, and became very fretful. She was seen by the family doctor who attributed the symptoms to dehydration and ordered fluids by mouth. The fever and abdominal distension subsided in a few days. Three weeks later, the baby was brought again to the family doctor because of further abdominal enlargement. Her general condition during this period was very good and there was no pyrexia, jaundice, anorexia, or vomiting, but the family doctor found hepatosplenomegaly and sent the child to the hospital.

She was admitted to a hospital where she remained for 2 weeks. From the information we had, routine examinations were negative except the chest x-ray which showed signs of bronchopneumonia. The baby was subsequently transferred to this hospital with a diagnosis of liver cirrhosis. A liver biopsy revealed tuberculous lesions. Typical tubercles, formed by epithelioid cells, were lying in the liver lobules or in the intralobular spaces. In many places there were areas of caseous necrosis with giant cell formation. Marked lymphocytic infiltration was seen around the tubercles. Numerous acid-fast bacilli were seen in sections of the lesions.

After the diagnosis had been established treatment was started with isoniazid and streptomycin. After the liver biopsy her condition suddenly deteriorated, with tachypnoea and grunting respirations.

The picture now was that of a very ill baby, pale and wasted, with a very distended abdomen (Fig.). There were few scattered rhonchi in both lungs. The liver was firm and extended 7 cm. below the costal margin. The spleen was firm and palpable 9.5 cm. below the left costal margin. A typical tuberculoma was present in the right optic fundus. The right ear was discharging purulent material. Lumbar puncture was not done. Mantoux test 1:1000 was negative. Hb 6.5 g./100 ml.,