Case report

Chronic malabsorption due to cryptosporidiosis in a child with immunoglobulin deficiency

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SUMMARY A case of fatal cryptosporidiosis in a child with primary immunoglobulin deficiency is described. This is always a serious complication in immunodeficient patients because there is no known effective therapy.

Intestinal infection by protozoan parasites collectively called ‘coccidia’ is an important cause of mortality in domesticated animals. In the past 10 years there have been sporadic reports of malabsorption due to coccidiosis in humans. Most of these cases have been associated with coccidia which were thought to belong to the genus Isospora, and many of the affected patients have been on immunosuppressive drugs. The taxonomy of the coccidia is now better understood, and there have been a few recent reports of chronic malabsorption due to organisms of the genus Cryptosporidium. The patients so far reported have either been on immunosuppressive drugs or had primary immunodeficiency disorders. One of these patients had primary immunoglobulin deficiency and we now report a second similar case where the disease was fatal.

Case report

This boy was born in Bermuda and was well until he developed septicaemia at 6 months of age. Hypogammaglobulinaemia was diagnosed during investigation of recurrent skin infections after he had moved to England at 3 years. He has since been maintained on weekly injections of gammaglobulin. He developed a painless swelling of the right knee at 5 years of age which spontaneously improved over the next two years. Examination revealed large tonsils and a spleen which was just palpable below the costal margin. Investigations at this time showed a normal blood lymphocyte count, a neutropenia (neutrophils, 950/μl) and an eosinophilia (eosinophils 900/μl). A five day faecal fat estimation was normal. The serum immunoglobulins were: IgG <25, IgA <4, IgM 236, and IgE <2 units/ml. The isohaemagglutinin titre (anti-A) was 1:64. Delayed hypersensitivity skin tests to Candida albicans and purified protein derivative (PPD) were positive. In vitro lymphocyte transformation to phytohaemagglutinin was normal.

At 6 years of age he complained of chronic steatorrhoea. A jejunal biopsy showed partial villous atrophy. Treatment with Mepacrine, metronidazole, and tetracycline did not help. At 8 years of age he still had chronic diarrhoea and his weight and height had fallen from the 50th to the 3rd percentile during the previous year. He was complaining of frequent vomiting, often associated with central abdominal pain. Investigation showed that he still had an eosinophilia but no longer had a neutropenia. The faecal fat was 30 g in 24 hours and he had a low serum calcium of 2.2 mmol/l, and a low serum folate of 38 ng/ml. The following tests were normal: lactose tolerance test, 14C deoxycholate breath test, and serum gastrin. The Lundh test showed a normal concentration of pancreatic enzymes in the jejunal aspirate. Bacterial cultures of a jejunal aspirate grew 104 organisms/ml. There were no abnormal bile acids in the stools. The barium meal and follow-through were normal. The jejunal biopsy was reported as normal. The liver function tests were abnormal with a raised

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Received for publication 23 June 1981.
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serum alkaline phosphatase of 25 KA units/100 ml and an aspartate transaminase of 56 IU/l.

During the subsequent six months he was given a variety of drugs—that is, Mepacrine, colistin, oxytetracycline, metronidazole, piperazine, thiobendazole, ampicillin, and erythromycin but none had any effect on the malabsorption and failure to grow. A gluten-free diet was also unhelpful. The diarrhoea was marginally improved by a low fat, high protein diet with additional medium chain triglycerides.

He remained a sickly child, intermittently attending school for the next two years. At 10 years of age he was readmitted as an emergency with severe watery diarrhoea. On examination there were signs of a left lower lobe pneumonia and there was marked clubbing of the fingers and toes. The liver was enlarged three fingers below the right costal margin. There was no splenomegaly. The severity of his diarrhoea resembled cholera and he required emergency intravenous therapy for water and electrolyte loss. He was given penicillin, ampicillin, and septrin and his diarrhoea subsided after a few days. The diarrhoea cleared up completely for about two weeks after this episode, although it subsequently returned. Another jejunal biopsy taken during this admission showed partial villous atrophy.

Our working diagnosis at this stage was allergic gastroenteropathy and he was tried on various diets, particularly a milk-free diet, without success. His last hospital admission at 12 years was for investigation of persistent diarrhoea, vomiting, and epigastric pain. By now he was severely wasted with a low serum albumin, calcium, magnesium, and zinc. He was given Vivonex but four weeks later developed another episode of cholera-like diarrhoea, which failed to respond to hydrocortisone, gentamycin, cloxacillin, or carbenicillin. Intravenous alementation was started but seven days later he developed jaundice and suddenly died of congestive cardiac failure. A jejunal biopsy taken a few days before death showed partial villous atrophy with parasites on the brush border (Figure). The necropsy findings suggested that the cause of death was acute pancreatitis. The jejunum had a particularly heavy infestation of coccidia, although there were many parasites in the ileum and a few in the large bowel.

Figure (a) Jejunal biopsy shows degenerate epithelium at surface and in crypts in association with numerous protozoal bodies. These are seen on the cell surface and within the cytoplasm. H and E, X 600 (original magnification). (b) Electron micrograph of jejunal biopsy. Cryptosporidium schizont, with almost mature merozoites in transverse section attached to surface of epithelium. X 27000 (original magnification).
Discussion

Four protozoal parasites collectively termed 'coccidias' are now known to be potentially pathogenic to man. These organisms are members of the sub-order Eimeria. The best known is Toxoplasma but Isospora and possibly Saracystis can also infect the intestine of man and cause malabsorption. More recently, cryptosporidial infection of the small and large bowel has been recognised in humans. Four cases have so far been reported. The first was associated with an acute enterocolitis in a 3 year old child which cleared spontaneously within a few weeks without therapy. The second was associated with severe watery diarrhoea in a man with bullous pemphigoid being treated with cyclophosphamide and prednisolone. He improved rapidly after the immunosuppressive drugs were withdrawn. The third case had a selective IgG deficiency from infancy and developed chronic malabsorption due to Cryptosporidium at 8 years of age. A wide variety of drugs, including pyrimethamine, sulphadiazine, and amprolium (which is a drug used in veterinary practice) did not help (E A Steck, personal communication). This boy still has severe malabsorption at the age of 12 years. The fourth patient was a renal transplant recipient on immunosuppressive drugs. We are aware of an additional fatal adult case in England who had normal immunoglobulin levels (ADM Bryceson, personal communication).

The host defence mechanisms against Cryptosporidium infection are unknown, although it is likely that antibodies are involved, as two of the reported cases have occurred in immunoglobulin deficient patients. Environmental factors may also play a part and contact with infected animals or living in certain parts of the world may be important.

From a practical point of view, Cryptosporidium infection should be considered in all patients with unexplained chronic malabsorption. It should be noted that jejunal biopsy specimens may appear normal, and that the small ovoid organisms can be easily missed on histological sections. In fact, the diagnosis was made in our case only on the sixth jejunal biopsy, although further sections taken in retrospect from a jejunal biopsy a year before death showed typical coccidial organisms. Once diagnosed the prognosis is very poor, particularly if immunosuppressive drugs cannot be incriminated. No satisfactory therapy has yet been found, although amprolium and other veterinary compounds are worth considering. Another possible approach is to give frequent infusions of the new types of intravenous gammaglobulin which will raise the serum gammaglobulin level towards normal. Now that cryptosporidiosis is an established human disease, additional investigation is needed into the host defence mechanisms against this organism in animals. There is also an urgent need to search for suitable drugs that will be effective in man.

We are grateful to the staff of the routine pathological service of Northwick Park Hospital for their help in managing this patient.

References

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Gut 1982 23: 80-82
doi: 10.1136/gut.23.1.80

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