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CLINICAL FEATURES OF DIARRHOEA IN CHILDREN CAUSED BY *CRYPTOSPORIDIUM PARVUM*

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Cryptosporidium parvum Tyzzer, 1912 is an important causative agent of diarrhoea in both developing and developed countries all over the world. It appears in sporadic cases and also epidemics; the largest known waterborne outbreak was in Milwaukee in 1993 struck 403,000 people (Cicerello H.G., Kehl K.S., Addiss D.G., Chusid M.J., Glass R.I., Davis J.P., Havens P. L. 1997: Epidemiol. Infect. 119: 53-60). Most of the sporadic cases involve small children and immunodeficient adults, especially AIDS patients.

This retrospective study reviews a five-year study of *C. parvum* enteritis in children hospitalised with diarrhoea at the Department of Infectious Diseases, Hospital České Budějovice, from 1992-1996. A total of 34 cases of *C. parvum* enteritis was recorded in this period. The mean age of the patients was 31 months, with a range from 5 to 93 months; 59% of them were male. Since the most interesting results were recorded in children under 3 years of age, the present study is focused on this age group. Altogether, 198 children of ages 2-36 months were examined, and the clinical course of enteritis due to *C. parvum* was compared with those caused by other pathogens or unidentified causative agents in this group. All children were examined clinically upon admission and daily until discharge. The following laboratory tests were performed routinely: biochemistry- estimation of creatinin, minerals, liver function tests, blood glucose and urine examination; haematology- complete blood count with a differential count; immunology- C-reactive protein test (CRP) and selective immunoglobulins and cell-mediated immunity tests; bacteriology- rectal swab examination, including rectal swab cultivation with a special emphasis for *Campylobacter jejuni*, and latex agglutination tests for rotavirus and adenovirus; parasitology- merthiolate iodine formaldehyde concentration (MIFC) and methylviolet-tartazine staining of smears for screening (Miláček P., Vítovec J., 1985: Folia Parasitol. 32: 50). Species identification was confirmed by PCR of SSU rRNA from oocysts isolated with species-specific primers (Slemenda S. 1993: Workshop on Microsporidiosis and Cryptosporidiosis in Immunodeficient Patients, České Budějovice, September 28 - October 1, 1993, Abstracts, p. 51).

In the whole group of 198 children, no causative agent was found in 92 cases. In 110 isolates from 106 patients, *C. parvum* was found in 11%. Other identified pathogens included rotavirus (13%), *Salmonella* (11%), *Campylobacter* (10%), enteropathogenic *Escherichia coli* (EPEC, 3%), adenovirus (3%), non-pathogenic protozoa (3%) and *Shigella* (1%) (Fig. 1). The age of 34 children hospitalised with *C. parvum* ranged from five months to eight years old (Fig. 2). Six of them were younger then 12 months and showed the following results:

History: the birth weight of the patients was 3.268 ± 453 g (2,500-4,350 g); 10 children had a premature birth. Two children had perinatal pathology, one had epilepsy.

Epidemiology: Our data are only anamnestic, no epidemiological investigation was performed. All cases were sporadic, patients came from both rural and urban areas. Some children had contact with calves (15%), or with other people having diarrhoea (26%). A part of the children came from families with a low socio-economic status. The seasonal distribution is shown in Fig 3.; *C. parvum* was found more often in the summer months.

Present illness: Mean duration of signs before admission was 2.8 ± 1.6 days, fever was present 1.9 ± 2.2 days. All children had predominately watery diarrhoea and almost all vomited (97%). Blood in the stool and abdominal cramps were determined in 9%.

Clinical course: Dehydration was present in 68% of the patients upon admission, but only 9% of them were severely dehydrated. Eighteen percent of children were mildly dystrophic. Fever lasted for about 1.9 ± 2.7 days (0-13) and diarrhoea for about 4.2 ± 3.1 days (0-13). The severity of diarrhoea was variable: the daily number of stools was 2 to 13; the stool was watery and in some patients voluminous. Diarrhoea lasted longer than 10 days in 9%; in 15% of patients the diarrhoea was only mild and resolved during 24 hours. Only 15% of the children vomited after admission. Problems with realimentation occurred in 12% of patients.

Laboratory tests: The erythrocyte sedimentation ratio (ESR) was elevated in only 12% and hypochromic anaemia was present in 32% of the children. White blood cells counts (WBC) were $9.13 \pm 3.0 \times 10^9/l$; 59% of patients had relative lymhocytosis and one-half had relative monocytosis higher than 10%. Serum glutamate oxalate and/or serum glutamate pyruvate transaminase (SGOT/SGPT) were elevated in 14.7%. With respect to immunology, we saw lower IgA and IgG in

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some children (not all were evaluated), and the CRP was not elevated. In patients tested for cell-mediated immunity, there was no decline in CD4+ lymphocytes and the immunoregulatory index (IRI) was 1.4-3.6. In rectal swabs, other pathogens (together with *C. parvum*) were also found: one case each of *S. enteritidis*, *Shigella*, rotavirus, *C. jejuni* with *S. enteritidis,* and in five children a massive *Candida albicans* infection.

Treatment: All patients had dietary and rehydration therapy: 38% received intravenous infusion followed by oral rehydration and the remaining had oral rehydration only. Antibiotics were given empirically (before etiologic diagnosis was made) only in the more severe cases with fever and dehydration, with cotrimoxazole and ampicillin being the primary drugs used. No specific anticryptosporidial therapy was tried. Hospitalisation lasted 2-35 (mean duration 11) days.

Cryptosporidiosis occurs in outbreaks or sporadic cases (Kendler J., Soave R. 1997: Curr. Op. Gastroenterol. 13: 64-70). Waterborne outbreaks are described elsewhere, especially in the USA and United Kingdom. The incidence of sporadic *C. parvum* enteritis varies from 1.9% in Italy (Brandonisio O., Marangi A., Panaro M. A., Marzio R., Natalicchio M.I., Zizzadoro P., De Santis U. 1996: Eur. J. Epidemiol. 12: 187-190) to 40.0% in rural parts of Southern Korea (Chai J.Y., Lee S.H., Guk S.M., 1996: J. Parasitol. 34: 113-119). Regardless of the geographic region, the incidence of cryptosporidiosis depends on several factors: rural or urban areas, socio-economic status, and age. Illness is more frequent in children, both in developing (Sherchand and Shresta 1996: J. Diarrh. Dis. Res. 14: 81-84; Miller K., Duran-Pinales C., Cruz-Lopez A., Morales-Lechuga L., Tarend., Enriquez F.J. 1994: Am. J. Trop. Med. Hyg. 51: 322-325; Okafor J.I. and Okunji O. 1996: J. Commun. Dis. 28: 49-55; Groves V.J., Lehmann D., Gilbert G.L. 1994: Epidem. Infect. 113: 491-499) and developed countries (Krause W., Abraham A., Lehman D. 1995: Appl. Parasitol. 36: 66-71; Brandonisio et al. 1996, op. cit.). A high prevalence was also found in elderly villagers (Chai et al., 1996, op. cit.). Asymptomatic carriage of cryptosporidia in immunocompetent and immunodeficient children is not well-documented. Six % of asymptomatic cryptosporidiosis in immunocompetent and 22% in immunodeficient were found in children 6.4% (Pettoello-Mantovani M., Di Martino L., Dettori G., Varjo P., Scotti S., Ditullio M.T., Gundalini S. 1995: Pediatr. Infect. Dis. J. 14: 1042-1047). Asymptomatic carriage was proven in developing countries, too (Okafor and Okunji 1996, op. cit.). In some rural populations with a high prevalence, *C. parvum* was often found concurrently in cattle (Chai et al. 1996, op. cit.), but waterborne infections seem to be more frequent.

In our group, the percentage of *C. parvum* diarrhoea in children of age of 0-3 years was surprisingly high, even in age under 12 months. The reason may be in the selection of patients: children suffering from diarrhoea from families with a higher socio–economic status are quite infrequently

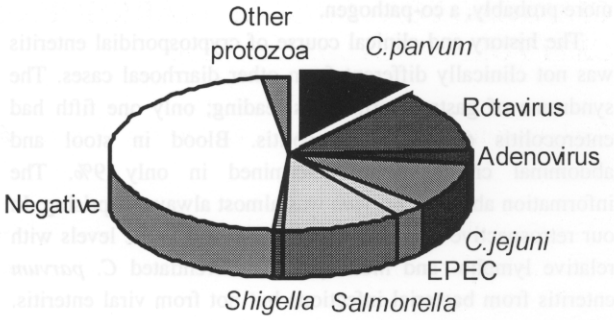

Fig. 1. Etiology of enteritis of 198 children 2-36 months old.

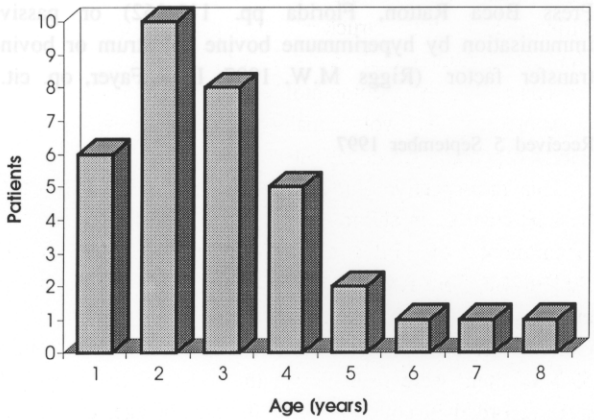

Fig. 2. Age distribution of 34 children infected with *Cryptosporidium parvum* and hospitalised in 1992 - 1996.

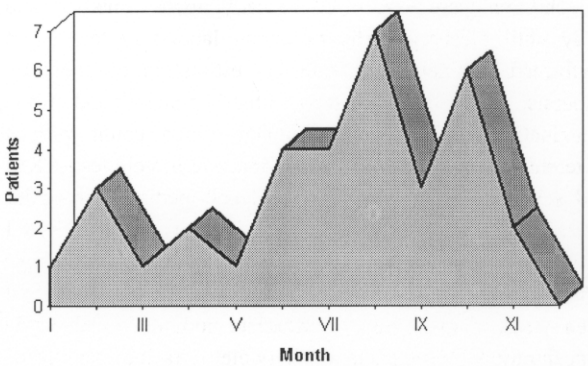

Fig. 3. Seasonal distribution of children with cryptosporidiosis in České Budějovice in 1992 - 1996.

hospitalised in this country because of the general availability of paediatric care, oral rehydration therapy, dietetics, etc. Our patients came predominately from families with a lower socio-economic status and, more often, from rural seats. In 12% of our patients, *C. parvum* was not the only etiologic agent, and other obligatory pathogens were found in stool samples, too. In these children, *C. parvum* was only an incidental finding or,

more probably, a co-pathogen.

The history and clinical course of cryptosporidial enteritis was not clinically different from other diarrhoeal cases. The syndrome of gastroenteritis was leading; only one fifth had enterocolitis or gastroenterocolitis. Blood in stool and abdominal cramps were determined in only 9%. The information about *C. parvum* was almost always surprising. In our retrospective study, low CRP, ESR and WBC levels with relative lympho- and monocytosis differentiated *C. parvum* enteritis from bacterial infections but not from viral enteritis. Therapies tried in the treatment of *C. parvum* diarrhoea included paromomycine, clarithromycine, azithromycine, octreotide, letrazuril (Blagburn B.L., Soave R. 1997: In: R. Fayer (Ed.), *Cryptosporidium* and Cryptosporidiosis. CRC Press Boca Ratton, Florida pp. 111-162) or passive immunisation by hyperimmune bovine colostrum or bovine transfer factor (Riggs M.W. 1997: In R. Fayer, op. cit.. pp.129-180). No specific therapy has been found to be consistently beneficial to children. In some patients, azithromycine brought a marked decrease in stool volume and frequency in the resolution of the diarrhoea (Hicks P., Zwiener R.J., Squires J., Savell V. 1996: Pediatr. 129: 297-300; Blanshard C., Shandond. C., Gazzard B.G. 1997: Int. J. Stud. AIDS 8: 124-129). In our patients, chemotherapeutics, if used, were chosen empirically and it was not necessary to change therapy after diagnosis of *C. parvum.*

C. parvum is an important causative agent of diarrhoea of small children in our region, even in children under 12 months. Laboratory findings of *C. parvum* (especially in small amounts) not always attests for the cause of illness. Enteritis due to *C. parvum,* as well as other pathogens, are clinically indistinguishable. *C. parvum* diarrhoea may be expected in some patients with low ESR, low WBC with relative lympho- and monocytosis and low CRP levels.

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