Hospitalization of Cuban children for giardiasis: a retrospective study in a paediatric hospital in Havana

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The medical records of the 185 children who, in 2007, were admitted to the Academic Paediatric Hospital ‘Centro Habana’, in the Cuban capital of Havana, because of giardiasis were analysed retrospectively. A standardized form was used to collect data on the socio-demographic characteristics, clinical features, laboratory diagnosis, treatment and length of stay of each child. Information on the 15 children who had incomplete medical records was excluded from the data analysis. Of the remaining 170 children, 85 (50.0%) were aged 1–4 years, 97 (57.1%) were male, and 106 (62.4%), 92 (54.1%) and 69 (40.6%) had presented with diarrhoea, vomiting, and/or abdominal pain, respectively. Most (91.2%) of the cases had been diagnosed by the microscopical examination of a duodenal aspirate, and the drugs that had been most used frequently were quinacrine and tinidazole, which had been given to 72 (42.4%) and 62 (36.5%) of the cases, respectively. The mean length of hospital stay was 4.9 days. Such information on the clinical characteristics of giardiasis among children living in an endemic area may be valuable to paediatricians and public-health officials who wish to screen for the disease.

Giardia lamblia (synonymous with *Giardia duodenalis* and *Giardia intestinalis*) remains one of the commonest pathogenic protozoans to be found in the human intestinal tract. In many developed countries, where the pathogen appears to be increasingly involved in diarrhoeal disease in day-care centres and water-associated outbreaks elsewhere, giardiasis is considered to be a

re-emerging disease (Thompson, 2000). Despite its generally high prevalence in developing countries, giardiasis often has a very focal distribution. The disease has been included in the ‘Neglected Diseases Initiative’ since 2004 (Savioli *et al.*, 2006).

In developing countries, *G. lamblia* infections are particularly common among children and pose a serious threat to child health and development, even though most infections with this protozoan are either asymptomatic or only involve a non-specific, mild and

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self-resolving illness. Unfortunately, some cases develop severe diarrhoea (with or without malabsorption syndrome), nausea, vomiting, weight loss (Escobedo *et al.*, 2010) and/or poor cognitive function and failure to thrive in early childhood (Berkman *et al.*, 2002). Recently, *G. lamblia* has also been implicated in post-infectious irritable bowel syndrome (Hanevik *et al.*, 2009) and chronic fatigue (Mørch *et al.*, 2009).

Although *Giardia* infection is relatively easy to diagnose and is curable, even with a single oral dose of an antiparasitic drug, its early detection and treatment form an important component of efforts to reduce transmission, the associated disease burden, and the risks of an infected individual developing chronic or intermittent symptoms (Escobedo *et al.*, 2010).

Many scientific questions about giardiasis remain unanswered, and the scientific world is only now attempting to catch up on decades of relative neglect. Our knowledge of the risk factors for, and clinical manifestations of, human giardiasis comes largely from studies either on travellers returning from countries where the disease is highly endemic or on major outbreaks. Surprisingly little is known about hospitalizations for the disease — or the clinical features of those hospitalized — in endemic countries, although hospital-admission data may form a valuable tool for assessing the epidemiology of a disease within a given population. The focus of the present study was on the clinical significance of giardiasis in Cuban children who had been hospitalized (presumably) because of the disease.

PATIENTS AND METHODS

Study Design and Setting

This retrospective study reviewed the records of those children who were admitted, with a diagnosis of giardiasis, to the Academic Paediatric Hospital 'Centro Habana' (APHCH), in Havana, Cuba, on any day in 2007. The 226-bed study

hospital, which is a government-funded and public facility, has already been chosen for several epidemiological studies because of the well-defined population that it serves (unpubl. obs.). It provides secondary and tertiary care and active ambulatory and emergency services, within all clinical and surgical specialities, for children from all over Cuba but mainly for children from the Centro Habana, Plaza, Cerro and Habana Vieja municipalities.

Data Collection

The staff in the APHCH's medical-records department was asked to provide a list (including the corresponding hospital registration number for each patient) of all the patients admitted in 2007 who had giardiasis (coded as A07-1) listed among their discharge diagnoses. The registration numbers were then used to obtain all the data held, as paper files, by the medical-records department, on each patient of interest. The files of interest were stored in the records department, for retrieval whenever needed.

Patients were only included in the study if: (1) their records appeared to be complete; (2) their symptoms recorded at presentation were consistent with giardiasis; and (3) *Giardia* cysts and/or trophozoites had been seen, by microscopy, in at least one faecal specimen or duodenal aspirate from the patient. For patients who had been admitted more than once in 2007, two admissions within a fortnight were considered to be a single admission.

The medical records of each patient who met all the inclusion criteria were studied in detail, with his or her socio-demographic characteristics (i.e., gender, age and address), medical history (i.e. date of admission, presenting signs and symptoms, and any co-diagnoses), laboratory results (i.e. results of the examinations of faecal samples and/or duodenal aspirates), prescribed treatment for giardiasis, and length of hospital stay all transferred to a standardized data-collection form.

Data Analysis

The data were analysed using version 6.04 of the Epi InfoTM software package (Centers for Disease Control and Prevention, Atlanta, GA), with χ^2 and Fisher's exact tests used, as appropriate, to make inter-group comparisons. A *P*-value of <0.05 was considered indicative of a statistically significant difference.

Ethical Considerations

The study protocol was approved by the APHCH's Ethics for Research Committee, on the condition that the authors maintained the confidentiality of the data retrieved from the patients' clinical records. Although four of the authors (A.A.E., P.A., M.A. and Y.S.) worked directly with the records, the names of the patients were excluded from the database used for the statistical analysis. Since the investigation was retrospective and based entirely on the results of the routine investigation of the patients by the staff of the APHCH, informed consent was not obtained specifically for the purposes of the present study.

RESULTS

Characteristics of the Study Population

During the study period, 8469 children were admitted to the APHCH, 1012 (11.9%) of them because of diarrhoea and 185 (2.2%) because of (parasitologically confirmed) giardiasis. Of the 185 cases of giardiasis admitted in 2007, 15 had incomplete medical records (nine) or missing medical records (six) at the time of the present study and were excluded from the data analysis. Of the 170 cases of giardiasis included in the final analysis (see Table), 97 (57.1%) were boys and 73 (42.9%) were girls ($P<0.01$). Thirty-seven (21.8%), 85 (50.0%), 42 (24.7%) and six (3.5%) of these cases were aged <1 year, 1–4 years, 5–12 years and >12 years, respectively.

Clinical Profile

At presentation (see Table), the commonest complaint was diarrhoea [seen in 106 (62.4%) of the 170 cases] followed by vomiting [92 (54.1%)] and abdominal pain [69 (40.6%)]. Urticaria, an unusual manifestation of giardiasis, was present in five of the cases (Table). No common source of the 170 giardial infections was identified.

Laboratory Evaluation

Giardiasis was confirmed by the results of the microscopic examination of either duodenal fluid [155 (91.2%) of the cases] or faecal samples [15 (8.8%) of the cases]. Only one or two faecal specimens had been requested from most of the cases (data not shown).

Treatment and Length of Stay

Antigiardial treatment (quinacrine, tinidazole, secnidazole or metronidazole) was given to all 170 cases (see Table), with quinacrine [72 (42.4%) of the cases] and tinidazole [62 (36.5%)] the drugs that were most frequently prescribed. The mean length of hospital stay was 4.9 days (range=1–16 days).

DISCUSSION

Although, in general, the prevalence of human infection with intestinal parasites has declined significantly in Cuba over the last few decades, infections with intestinal protozoa, especially *G. lamblia*, remain among the most common infections diagnosed (Rojas *et al.*, 2008). According to the last national survey, the overall prevalence of *Giardia* infection in the human population is about 7.2% (E. Sanjurjo, unpubl. obs.); although the evidence to support this belief seems largely anecdotal, clinical giardiasis is generally considered to be an important public-health problem in Cuba, placing a large burden on both diagnostic and treatment services in the country's

TABLE. Characteristics of the 170 patients with complete clinical records who, in 2007, were admitted to the Academic Paediatric Hospital 'Centro Habana' with *Giardia* infection

Characteristic	No. and (%) of patients
GENDER	
Male	97 (57.1)
Female	73 (42.9)
AGE (years)	
<1	37 (21.8)
1–4	85 (50.0)
5–12	42 (24.7)
>12	6 (3.5)
LENGTH OF HOSPITAL STAY (days)	
<2	1 (0.6)
2–4	89 (52.4)
>4	80 (47.1)
CLINICAL FEATURES	
Diarrhoea	106 (62.4)
Vomiting	92 (54.1)
Abdominal pain	69 (40.6)
Fever ($\geq 38^{\circ}\text{C}$)	39 (23.1)
Weakness	25 (14.7)
Dehydration	20 (11.8)
Poor oral intake	18 (10.6)
Weight loss	6 (3.5)
Urticaria	5 (2.9)
METHOD USED TO CONFIRM GIARDIASIS	
Examination of duodenal aspirate	155 (91.2)
Examination of faecal sample(s)	15 (8.8)
CHEMOTHERAPY	
Quinacrine	72 (42.4)
Tinidazole	62 (36.5)
Secnidazole	28 (16.4)
Metronidazole	8 (4.7)

healthcare institutions. Higher prevalences have been recorded among young children attending day-care centres and primary schools in Cuba (Núñez *et al.*, 1999; Arencibia *et al.*, 2001; Mendoza *et al.*, 2001; Escobedo *et al.*, 2007). Among young children, a lack of faecal continence before toilet training, frequent person–person and hand–mouth contact, poor standards of hygiene, an immature immune system and the high probability that any *Giardia* infection will be a primary infection presumably combine to increase the probabilities of both *Giardia* infection and symptomatic giardiasis (Rojas *et al.*, 2008). In endemic areas, the incidence of giardiasis tends to peak in children aged 2–3 years and then to

decrease with increasing age, perhaps as the result of acquired immunity (Núñez *et al.*, 1999) and/or improving standards of hygiene. In a community-based study conducted in the Cuban province of Pinar del Río, Escobedo *et al.* (2008*b*) found children aged <6 years to be at a more than 3-fold higher risk of *Giardia* infection than children aged 6–10 years. Elsewhere in Cuba (Núñez *et al.*, 1999) and in Kenya (Chunge *et al.*, 1991), Israel (Fraser *et al.*, 1997), Brazil (Pereira *et al.*, 2007) and New Zealand (Snel *et al.*, 2009), relatively high risks of *G. lamblia* infection have been detected in children, at least after the first year of life.

In the present study, significantly more of the giardiasis cases identified were boys than

girls. A similar predominance of males was seen by Keiser *et al.* (2002), in a community-based study in Côte d'Ivoire, where the prevalence of *Giardia* infections among the male participants was found to be double that among the female. In *Giardia* surveillance in the U.S.A. (Yoder and Beach, 2007), male cases have been found to outnumber the female in every age-group considered except the youngest (<1 year) and the eldest (>59 years). A male predominance among giardiasis cases has also been reported in Ontario, Canada (Greig *et al.*, 2001). Such a gender bias has not, however, been seen everywhere. The boys attending the Cuban day-care centres investigated by Núñez *et al.* (1999), for example, were found to be no less or more likely to harbour *Giardia* infection than their female playmates. These divergent results could be a consequence of gender-associated differences in exposure to *Giardia* (with the behaviour and recreational exposure of boys differing from those of girls in some settings) and/or gender-associated differences in susceptibility to infection post-exposure. Sex-associated hormones may modulate the immune responses of a mammalian host and thus directly influence the outcome of parasite infection (Roberts *et al.*, 2001). The possibility that females are, in general, better protected against giardial infection and/or the development of symptomatic giardiasis than their male counterparts deserves further investigation.

The clinical manifestations of giardiasis are extremely variable and may overlap with those of a wide range of infectious and non-infectious gastro-intestinal disorders. Most of the cases of the disease investigated in the present study presented with diarrhoea. This common feature of symptomatic giardiasis (Pereira *et al.*, 2007; Dib *et al.*, 2008; El Guamri *et al.*, 2009) may be characteristic of acute infection and is often short-lived and self-limiting, although it may become chronic. In Cuba, unfortunately, little is known about the infectious agents affecting hospitalized patients with diarrhoea. Of the

hospitalized children investigated by Núñez *et al.* (2003), in another paediatric hospital in Havana, 9% were found infected with *Giardia*, including 5% of the children with diarrhoea. In similar studies in Greece (Kafetzis *et al.*, 2001) and India (Saha *et al.*, 2008), the prevalence of *Giardia* infection among hospitalized children with diarrhoea has been found to be relatively low.

Abdominal pain is also frequently reported in symptomatic patients with giardiasis (Aparicio Tijeras *et al.*, 2004). In their recent observational study in Peshawar, Pakistan, Younas *et al.* (2008) detected *Giardia* infection in 74 (31%) of 239 children with recurrent abdominal pain. When Yakoob *et al.* (2005) investigated dyspeptic patients who attended the gastro-enterology department of the Aga Khan University Hospital in Karachi, Pakistan, they found that 68 (71%) of the 96 patients with giardiasis complained of abdominal pain ($P=0.02$) and that 28 (29%) of the giardiasis cases had diarrhoea ($P=0.005$). Concomitant *Giardia* and *Helicobacter pylori* infections may often play an important role in the development of recurrent abdominal pain in children (Zeyrek *et al.*, 2008). Compared with the healthy children used as controls, Turkish children with recurrent abdominal pain were not found significantly more likely to be infected with *H. pylori* or *Giardia* but they were found significantly more likely to be co-infected with the two pathogens (22.4% *v.* 6.8%; $P=0.002$; Zeyrek *et al.*, 2008).

Although the possible association between *Giardia* infection and some allergic manifestations has already been discussed (Veronesi *et al.*, 1983; Nenoff *et al.*, 2006), the discovery that five giardiasis cases investigated in the present study had urticaria was a surprise. The subjects of the present study, had, however, all been hospitalized and therefore generally represented children with relatively severe giardiasis, among whom urticaria may be relatively common. In diarrhoeal patients in general, the impaired function of the

gastro-duodenal barrier may increase the possibility of chronic urticaria (Buhner *et al.*, 2004). In immunocompetent but athymic mice, *Giardia* infection caused a significant increase in small intestinal (but not gastric or colonic) permeability that correlated with trophozoite colonization (Scott *et al.*, 2002). In humans, damage to the intestinal wall resulting from *Giardia* infection may also increase intestinal permeability (Dagci *et al.*, 2002). In Cuba, high prevalences of *Giardia* infection have been seen among patients with urticarial vasculitis (Martínez-Rodríguez *et al.*, 1992). In the present study, however, the observed urticaria cannot be unequivocally attributed to *Giardia* infection, as the aetiology of this allergic disturbance might lie in other concomitant and missed diagnoses.

None of the children included in the present study was recorded as having acute or chronic malnutrition and <15% were recorded as having dehydration, even though malnutrition and dehydration have been found to be common features of paediatric giardiasis in many other settings (Adam, 2001). In Cuba, however, access to hospitals is relatively easy and free of charge, so children tend to receive medical care before such complications develop.

The easy availability of duodenal aspiration in the hospital at which the present study was based appears to have resulted in an over-reliance on duodenal aspirates for the diagnosis of giardiasis. Almost all of the children included in the present study had been confirmed as giardiasis cases by the microscopical examination of such aspirates, even when it remains unclear whether this method is more (Kamath and Murugasu, 1974; Rosenthal and Liebman, 1980) or less sensitive (Goka *et al.*, 1990) than the examination of faecal samples (which is non-invasive and remains the standard procedure for most intestinal parasites). The examination of wet mounts of unconcentrated samples may offer generally low sensitivity but the APHCH lacked the facilities needed for sample concentration (such as formalin-ether or Faust flotation) in 2007.

Sample concentration would increase sensitivity without much extra input. Despite slightly increasing the time needed for a diagnosis, it is simple and can be applied easily in a laboratory with quite basic equipment and staff training.

The examination of a single faecal specimen/patient is generally considered insufficient for the diagnosis of giardiasis (Hiatt *et al.*, 1995) because the shedding of *Giardia* cysts or trophozoites is often intermittent or at such low levels that it is difficult to detect (Hiatt *et al.*, 1995; Cartwright, 1999). Ideally, a duodenal aspirate should be collected from a suspected case of giardiasis who has been found *Giardia*-negative over the recommended three faecal examinations (Wolfe, 1992), and checked for *Giardia*. The routine use of duodenal aspiration as the initial method for the detection of a *Giardia* infection cannot be recommended even though, at the APHCH in 2007, it made diagnosis quicker (than the examination of multiple faecal samples/patient) and therefore, presumably, generally reduced the length of each giardiasis case's hospital stay.

In the present study, the *Giardia*-infected children were treated using one the four drug regimens (based on metronidazole, tinidazole, secnidazole or quinacrine) approved for giardiasis in the Cuban national therapeutic guidelines (Anon., 2006). Curiously, although these guidelines recommend the use of metronidazole for first-line treatment [the drug has been found to achieve parasitological cure in 75%–100% of giardiasis cases (Escobedo and Cimerman, 2007)], this drug was only used rarely to treat giardiasis cases at the APHCH in 2007. Quinacrine and tinidazole were the drugs most frequently used to treat giardiasis at the APHCH in 2007, probably simply because they were available at the time of the diagnoses and considered as effective as metronidazole (Escobedo *et al.*, 2003; Cañete *et al.*, 2006). Tinidazole is also slightly cheaper [U.S.\$40/1000 children treated compared with U.S.\$45/1000 for metronidazole (Chandy

and McCarthy, 2009)], generally well tolerated, clears diarrhoea quickly (Gazder and Benerjee, 1978) and can be used to treat giardiasis as a single oral dose (Escobedo and Cimerman, 2007), which has the potential to improve compliance.

The length of hospital stay has many implications both for the patient and the public-health service. For the latter, these include impacts on financial resources, staffing and bed availability. Stay length has been repeatedly used as an indicator of efficiency in in-patient care. In the present study, the mean hospital stay of a giardiasis case was 4.9 days, comparable with the corresponding 4 days found in the U.S.A. (Lengerich *et al.*, 1994) and the 3 days (overall mean) or 4 days (mean for cases aged <5 years) recorded in Scotland (Robertson, 1996). Cases may be discharged while still receiving chemotherapy (once they have shown a clinical response). The diarrhoea associated with giardiasis generally resolves a few days post-treatment (Ortiz *et al.*, 2001; Rossignol *et al.*, 2001), occasionally before parasitological cure has been achieved (Escobedo *et al.*, 2008a).

No attempt was made to evaluate, in the present study, the financial costs of the hospitalization of children with giardiasis but such costs have been explored in some other investigations, with interesting results. Robertson (1996) estimated the annual hospitalization costs associated with severe giardiasis in Scotland to be in excess of £31,000 (about U.S.\$50,000 in 1996) while, more recently, notified cases of human giardiasis in New Zealand were estimated to cost the health system N.Z.\$987,000 (about U.S.\$500,000) each year (Snel *et al.*, 2009). The true economic costs of human giardiasis in Scotland and New Zealand are probably much higher than these two estimates indicate, however, since the estimates take no account of non-notified cases of the disease.

The present results need to be interpreted with caution, given the limitations of the study on which they are based. Firstly, the

results are based on a retrospective review of medical records that may not be comprehensive. Secondly, a hospital-based study can only provide limited information about the prevalence of giardiasis in the general community, partly because children with giardiasis who present at a hospital are not likely to be representative of children with giardiasis in the general population, with many milder cases never presenting at a health facility or only seeking care from a general practitioner or a centre for primary healthcare. Thirdly, the diarrhoea episodes (and other symptoms) seen in many of the children investigated in the present study could not be unequivocally attributed to giardial infection, partly because the tests necessary to exclude other causes were often never conducted. The only cases to have faecal samples checked for bacterial pathogens, by culture, were those who were suspected clinically of having infections with such bacteria, and no attempt was made to check any child for viruses because the laboratory resources that were available were too limited. Finally, it was not possible to follow-up the children investigated after their hospital discharge and so assess either the development of 'residual morbidity' related to *Giardia* infection or the frequency of treatment failure. Despite these limitations, the present results provide valuable insight into the clinical manifestations of paediatric giardiasis in an endemic area, the age-prevalence relationship of the condition (at least among children), and the burden posed by giardiasis on in-patient services in Cuba. Although the data analysed are inevitably referral- and access-biased, they provide useful information on *Giardia*-related morbidity in the study area and the role played by hospital-based paediatric services in the management of giardiasis in Havana.

The present results may help physicians practising in endemic areas to diagnose cases of symptomatic giardiasis (particularly paediatric cases) promptly and accurately, although the general non-specificity of the

signs and symptoms of this disease hamper its diagnosis. It is evident that, at the APHCH (and, presumably, many similar hospitals in Cuba), stronger efforts should be made to detect *Giardia* and/or other enteropathogens, partly by checking at least three faecal samples/patient.

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