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TOXOPLASMOSIS IN CHILDREN OF THE SOUTH BAČKA REGION, SERBIA: A NEW LIGHT IN THE PUBLIC HEALTH PERSPECTIVE

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Abstract - In this study the presence of anti-Toxoplasma IgM and IgG antibodies in sera of 245 children, aged 1 to 18 years, was determined. In the eldest group (15-18), 29.2% of the sera were positive for the IgG antibody. *Toxoplasma gondii* infection in pregnant women and immunosuppressed patients produces severe consequences, while in immunocompetent individuals it is considered asymptomatic and latent. Recent emerging links to mental disorders has shed a completely new light on the public health view of this common infection. It calls for a new approach in the prevention and screening of a population, children being the target group.

Key words: Toxoplasma gondii, children, public health, seroprevalence

INTRODUCTION

Toxoplasmosis is a widely spread infection, with approximately one third of the world's population being infected (2.5 billion people worldwide, Centers for Disease Control and Prevention, 2008), thus easily earning the title of cosmopolitan infection (Pappas et al., 2009.). Its causative agent, a protozoan parasite, *Toxoplasma gondii*, is considered to be among the most successful known parasites, representing an excellent example of a biologically successful host-parasite co-evolution.

Toxoplasma gondii is a protozoa belonging to the phylum Apicomplexa, order Coccidia and family Sarcocystidae. It was first described in 1908 by Nicolle and Manceaux and Splendore, independently, in gundi (*Ctenodactylus gundi*), a North African rodent (Ferguson, 2009). The name is derived from its crescent shape and the animal form from which it was first isolated. Wolf and Cowen (1937) established *T. gondii* as a potential cause of neonatal encephalitis in humans, and it was subsequently found that the infection could be congenitally acquired (Paige et al., 1942). However, the full life-cycle was not completely understood until the 1970s (Frenkel et al., 1970, Hutchinson et al., 1969).

Although felids are definitive hosts of this parasite (where it multiplies sexually in the gut), it needs intermediate hosts in any homoeothermic terrestrial vertebrate (where it forms cysts in muscular and neural tissues). In its life-cycle, *T. gondii* takes several forms: oocysts, tachyzoites (fast-growing), and bradyzoites (slow-growing, the most common form being confined to neurons, glial cells and cysts in the brain (Montoya and Leisenfeld, 2004).

Toxoplasmosis is a highly transmissible disease, spread through the accidental ingestion of oocysts shed by hosts in the environment, or tissue cysts in undercooked meat. Thorough washing of fruits and

vegetables, avoiding the drinking of untreated water and eating of under-cooked meat, together with basic sanitary measures (hand-washing), are the principal preventive measures. Contact with cats is also identified as a risk factor and attention when handling their litter boxes is advised (Miró et al., 2008).

In immunocompetent hosts, the infection is usually considered asymptomatic or passes with spontaneously resolved symptoms – fever, malaise and lymphadenopathy (Hill et al., 2007). The exceptions are pregnant women, where newly acquired infection can produce significant damage to the developing fetus, causing mental retardation, blindness, epilepsy and death. Even when congenital toxoplasmosis is asymptomatic at birth, it can produce ocular problems later in life (Petersen, 2007). On the other hand, in immunocompromised patients, both iatrogenic and pathogenic (organ transplant, AIDS), acute reactivation may occur, typically presenting with encephalitis, ocular disease, and lymphadenopathy (Montoya and Leisenfeld, 2004).

Recent data have shown the emerging link between *T. gondii* seropositivity and certain mental disorders: schizophrenia (Torrey et al., 2007), personality disorders (Hinze-Selch et al., 2010), suicide attempts (Arling et al., 2009, Yagmur et al., 2010), even car accidents (Flegr et al., 2002; Yereli et al., 2006). A recent ecologic analysis (Lester, 2010) found an association between estimated *T. gondii* seropositivity and national average suicide rates across twenty European nations.

While it is still just a correlation, and possible molecular mechanisms remain to be elucidated, these findings change the perspective and call for a revision in the treatment of so-called "asymptomatic" infections, especially from the public health standpoint.

Recent findings further imply a more thorough screening of *T. gondii* antibodies, not only in pregnant women, as done up to now in many European countries, but in children as well. Children are particularly vulnerable to toxoplasmosis due to their close contact with soil and animals, and can serve as an optimal indicator of the presence of this parasite in the population. Furthermore, acquiring knowledge about the possible infection early in life provides the opportunity of preventing the negative health consequences, which appear to be continuously emerging in the literature (Toporovski et al., 2012).

General seroprevalence of toxoplasmosis varies greatly throughout the world, ranging from only a few percent in some regions (Switzerland, China) to more than 60% of infected individuals (Brazil, France) (Pappas et al., 2009).

With all this in mind, the aim of our study was to determine the levels of anti-toxoplasmosis IgM and IgG antibodies in children in the South Bačka region of Serbia.

MATERIALS AND METHODS

The prevalence of anti-toxoplasmosis antibodies was examined retrospectively in a population of 245 children (age 1-18), divided into three age groups: preschool children (age 1-6), primary school children (age 7-14) and high school students (age 15-18). Data were retrieved from the Protocol of Virology Analyses, Center of Virology, at the Institute of Public Health of Vojvodina. The analyzed group included 133 children of preschool age, 78 primary school children and 34 high school students. All of them were directed by primary care physician or pediatricians to perform virology analyses in order to confirm or exclude the suspected toxoplasmosis diagnosis.

To determine the presence and levels of *T. gondii*-specific IgM and IgG antibodies in serum samples, commercially available ELISA kits were used (Euroimmun, Germany). The assays were performed according to the manufacturer's instructions.

For statistical significance, the χ^2 test was done.

RESULTS

Our results indicate a significant presence of toxoplasmosis in all age groups of analyzed children. The presence of IgM antibody, an indicator of acute infection, was detected in 17.3% of preschool children, 15.4% of primary school children, and 23.5% of high school students. Differences among the groups were not statistically significant. Among children suspected of toxoplasmosis, it appears that all age groups were more or less equally exposed to the parasite. The IgG antibody, however, was present in significantly the highest percent in the eldest group (15-18 years old), where 29.2% tested positive. This was expected, since this category of antibody reflects previous exposure to the pathogen, so it is quite logical for IgG presence to rise with age.

DISCUSSION

Data on toxoplasmosis in children are generally scarce. Since congenital toxoplasmosis has severe consequences, the primary focus of Toxoplasma screening tests in most countries are pregnant women and women in the generative age (15-45 years), and these data are usually used to estimate the general seroprevalence in a population (Pappas et al., 2009). However, with the recent developments in research into *T. gondii* and psychiatric disorders, a so-called "asymptomatic" or "latent" infection is likely to be proved very important and not at all without symptoms as previously thought. This will inevitably produce changes in public health treatment of this parasitic infection, and undoubtedly emphasize the importance of screening in all age groups, primarily children.

The seroprevalence of *T. gondii* is constantly changing worldwide as a result of complex environmental, socioeconomic and health-related practices. Of major influence are factors such as the presence or absence of cats or dogs, contact with soil, food habits (consumption of raw or improperly cooked meat or vegetables), and climatic as well as socioeconomic conditions (use of untreated water) (Montoya and Liesenfeld, 2004.; Jones et al., 2009.; Cenci-Goga et al., 2011).

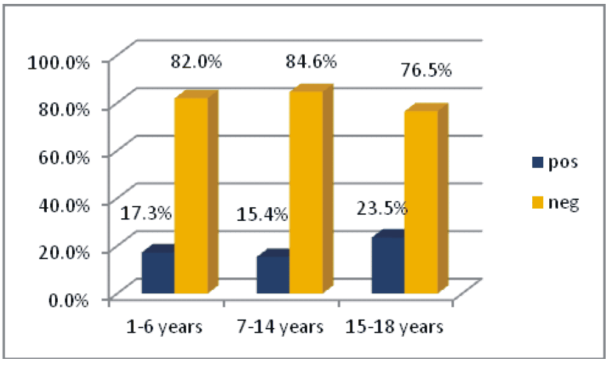

Fig. 1. The presence of Igm antibiodies in sera if children in three age groups: 1-6; 7-14 and 15-18 years old. Data are given in percentile; pos - positive; neg - negative.

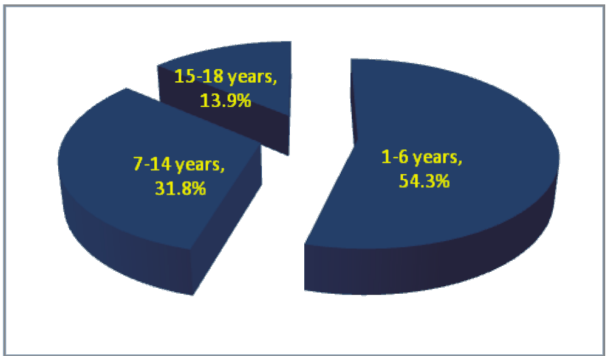

Fig. 2. Age distribution of children in the sample analyzed for IgM antibodies.

Although it seems likely that exposure to cat feces or contact with soil or water contaminated by *Toxoplasma* oocysts is one of the most important factors associated with *Toxoplasma* infection, other factors must not be neglected. The presence of the parasite in the environment is determined by many factors, among which climate has a substantial role. Thus, the presence of cats *per se* in some areas of the world does not necessarily mean high incidence of the disease. A good example is a relatively low regional seroprevalence in Qatar – 25% (Abu-Madi et al., 2008), with a large population of cats (it is estimated that 2 million cats live in Qatar). Socioeconomic factors are not to be neglected, but are not always the only determinant. China, for example, exhibits one of the lowest prevalence rates worldwide, being below 1% in the province of Shangdong (Chen et al., 2005).

Small children are particularly vulnerable to toxoplasmosis due to their close contact with soil and pets, and their habit of eating various unwashed raw foods if not supervised. Teenagers as well are at risk, and have to be educated properly in order to protect them from the infection.

In developed countries, the prevalence of *Toxoplasma* infection among primary schoolchildren is generally low, with a range of 0.0% in Japan to 11.0% in Ireland (Suzuki at al., 1988; Taylor et al., 1997). Seroprevalence in other parts of the world varies greatly: in Slovakia (20.5%), Iran (20.9%), Indonesia (50.0%) and Brazil (68.4%) (Souza at al., 1987; Konishi et al., 2000; Sharif et al., 2010). In Africa alone, seroprevalence in children ranges from 0% in Swaziland (Liao et al., 2009) to 63.1% in West Africa's São Tomé (Fan et al., 2012).

On the global level, Serbia and the Balkans in general, has a moderate incidence (in the range of 20-40%). which is precisely the middle category on the ranking established by Pappas et al. (2009). For the northern province of Vojvodina, the stable high prevalence in Hungary (almost 60% for the mid-1990s) (Szenasi et al., 1997), is worth considering.

It must be mentioned that for most countries seroprevalence in a population is based on data of pregnant women and women in the generative age, since a routine prenatal screening of *Toxoplasma* is done, and it is has been known for long that sex differences are not significant (Beverley et al., 1976). However, these data cannot be used to estimate seroprevalence in children. From a public health standpoint, children are the right target group to investigate toxoplasmosis prevalence. Data collected from this age group can be used to estimate whether toxoplasmosis threatens the health of a population as a whole, and as a reference for evaluating the need for community interventions.

With the recently emerging link of latent toxoplasmosis to mental illnesses (Hurley and Taber, 2012.) and suicide rates (Ling et al., 2011), the careful and adequate screening of *T. gondii* presence in a population becomes even more important. Although the mechanism of the influence on mental health is not completely understood, recent studies indicate that *T. gondii* cysts in brain may be able to directly influence the synthesis of dopamine, as this parasite has two genes encoding tyrosine hydroxylases (the rate-limiting step in dopamine synthesis) (Gaskell et al., 2009), disturbing the fragile balance of neurotransmitters in the brain.

In the innate immune response to *T. gondii*, monocytic, natural killer and CD8(+) T cells play an important role, and a complex interplay of immunomediators such as tumor necrosis factor α (TNF-α), several interleukins (IL-2; IL-12; IL-23) and interferon γ (IFNγ) has been revealed. Extensive research has been done to elucidate the pathophysiology (Miller et al., 2009) as well as for possible vaccine development (Sa et al., 2013).

While prevention of toxoplasmosis is still the best solution, new options for the treatment and diagnosis of the infection are constantly been searched for. In the design of new drugs, advances in chemical, proteomic and genetic tools are used and have led to the development of new approaches that specifically influence parasite survival and propagation inside the host (e.g. inhibition of proteolytic enzymes, Li et al., 2012) or block the process of host cell invasion (Hall et al., 2011). Aside from the routinely used ELISA tests, diagnostic techniques also include Western blot analysis and PCR technology that have greater sensitivity and precision, are of the utmost importance especially in congenitally acquired toxoplasmosis (Yamada et al., 2011; Magi and Migliorini, 2011).

CONCLUSIONS

Toxoplasma gondii is a pathogen known to science for over a century. Apart from being spread all over the world and infecting practically every warm-blooded terrestrial vertebrate, the effects of its presence in the human body are still not fully understood. While it is known that the infection in pregnant women and immunosuppressed patients produces severe conse-

quences, the infection of immunocompetent individuals was considered asymptomatic and latent for decades. Recent emerging links to mental disorders has shed a completely new light on the public health view of this common infection. It calls for a new approach in the prevention and screening of a population in which children are the target group.

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