Early Human Development 88 (2012) 879–884

Contents lists available at SciVerse ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Slower postnatal motor development in infants of mothers with latent toxoplasmosis during the first 18 months of life

Šárka Kaňková [a,*], Jan Šulc [b], Romana Křivohlavá [c], Aleš Kuběna [a], Jaroslav Flegr [a]

[a] Department of Philosophy and History of Science, Faculty of Science, Charles University in Prague, CZ-128 44 Prague 2, Czech Republic
[b] Centre of Reproductive Medicine, Nad Bud'ánkami II/24, CZ-150 00 Prague 5, Czech Republic
[c] Laboratory of Natural Immunity, Department of Immunology and Gnotobiology, Institute of Microbiology, v.v.i., Academy of Sciences of Czech Republic, CZ-142 20 Prague 4, Czech Republic

ARTICLE INFO

Article history:
Received 22 March 2012
Received in revised form 28 May 2012
Accepted 3 July 2012

Keywords:
Parasite
Immunity
Motor development
Toxoplasma
Retardation

ABSTRACT

Toxoplasmosis, a zoonosis caused by a protozoan, *Toxoplasma gondii*, is probably the most widespread human parasitosis in developed countries. Pregnant women with latent toxoplasmosis have seemingly younger fetuses especially in the 16th week of gestation, which suggests that fetuses of *Toxoplasma*-infected mothers have slower rates of development in the first trimester of pregnancy. In the present retrospective cohort study, we analyzed data on postnatal motor development of infants from 331 questionnaire respondents including 53 *Toxoplasma*-infected mothers to search for signs of early postnatal development disorders. During the first year of life, a slower postnatal motor development was observed in infants of mothers with latent toxoplasmosis. These infants significantly later developed the ability to control the head position ($p = 0.039$), to roll from supine to prone position ($p = 0.022$) and were slightly later to begin crawling ($p = 0.059$). Our results are compatible with the hypothesis that the difference in the rates of prenatal and early postnatal development between children of *Toxoplasma*-negative and *Toxoplasma*-positive mothers might be caused by a decreased stringency of embryo quality control in partly immunosuppressed *Toxoplasma*-positive mothers resulting in a higher proportion of infants with genetic or developmental disorders in offspring. However, because of relatively low return rate of questionnaires and an associated risk of a sieve effect, our results should be considered as preliminary and performing a large scale prospective study in the future is critically needed.

1. Introduction

Probably the most widespread human parasitosis in developed countries is caused by the protozoan *Toxoplasma gondii*. Life-long latent toxoplasmosis is usually considered to pose no health threat to immunocompetent persons; however, it is accompanied by specific changes in the psychomotor performance, behavior and personality profile [1–3]. The most serious is congenital toxoplasmosis; in pregnant women in the acute phase of the infection, the parasite can infect the placenta and, after a lag period, also the fetus. About 20% of infants with congenital infection have severe disease. Approximately 70% of them are asymptomatic at birth but can develop clinical symptoms later. For example, they have slower neurological and mental development and can also later develop hearing and vision impairments, the latter being typically associated with chorioretinitis [4].

Neither pathological changes nor health damage was reported in neonates born to mothers with latent toxoplasmosis. Kimball et al. [5] speculated on possible effects of latent toxoplasmosis on the risk of abortion; however, this speculation was not confirmed in later studies [6,7]. Pregnant women with latent toxoplasmosis were reported to have seemingly younger (less developed) fetuses, especially at the 16th week of pregnancy [8,9]. Two different immunological hypotheses were suggested to explain this effect of toxoplasmosis on pregnancy. One assumes that the changes in the immune system could delay the implantation of the blastocyst in multiparous women with toxoplasmosis. The other posits that *Toxoplasma* could weaken or switch off the mechanism of spontaneous abortions, which is under normal conditions responsible for the elimination of embryos with developmental defects and therefore with a (statistically) slower fetal growth rate. The latter hypothesis was recently supported by the observed increase in the secondary sex ratio in children of women with latent toxoplasmosis [10]. The probability of the birth of a boy increased up to 0.71, which means that about 250 boys were born for every 100 girls to women with moderate concentrations of anti-*Toxoplasma* antibodies (and therefore probably with recent but already latent infection). This effect of latent toxoplasmosis was later confirmed in experimentally infected mice [11]. Mice with toxoplasmosis produced a higher sex ratio (expressed as the proportion of males in the offspring) than

* Corresponding author at: Department of Philosophy and History of Science, Charles University, Viničná 7, CZ-128 44 Prague 2, Czech Republic. Tel.: +420 221951821; fax: +420 224919704.
E-mail address: kankova.sarka@gmail.com (Š. Kaňková).

0378-3782/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.earlhumdev.2012.07.001

controls, in the early phase of latent infection. A recent study [12] showed significant modifications of cytokine production and modulation of some parameters of the immune response during latent toxoplasmosis. These results for the infected mice are in accordance with the hypothesis that the increased probability of the birth of male offspring in *Toxoplasma*-infected mice and humans might be just a nonadaptive side effect of *Toxoplasma*-induced immunosuppression. Similarly, the immunosuppression could also be responsible for the observed longer pregnancy in mothers with latent toxoplasmosis [9], either due to reduced implantation potential of the fertilized ovum in immunosuppressed females [13] or to higher probability of survival of fetuses with genetic or developmental disorders [8,9] including those with chromosomal aberrations. This can explain the extremely high prevalence of latent toxoplasmosis in mothers of children with Down syndrome (about 84% vs. 32% in controls) [14].

If *Toxoplasma* actually allows the development of embryos that would be miscarried when born by *Toxoplasma*-negative mothers, then differences in the rates of postnatal development should be probably observed between infants of infected and non-infected mothers. If the children with genetic or developmental disorders are overrepresented in the offspring of infected mothers, then we should expect slower rates of early postnatal development in children of mothers with latent toxoplasmosis in comparison with those of *Toxoplasma*-negative mothers. The aim of the present study is to search for signs of delayed postnatal motor development in children of mothers with latent toxoplasmosis within the first 18 months after delivery using a questionnaire survey among 351 mothers tested for latent toxoplasmosis during pregnancy.

2. Material and methods

2.1. Subjects

The experimental set consisted of women from two private clinics (Centres of Reproductive Medicine in Prague 5 and Prague 8). The experimental design was a retrospective cohort study. All study subjects were sent a questionnaire form to be filled out at home. Clinical records contained data on maternal age, newborn's sex and results of the serological test for toxoplasmosis at about the 16th week of pregnancy. The concentration of anamnestic titres of IgG antibodies against *Toxoplasma* was determined by the indirect immunofluorescence test (IIFT) at dilutions between 1:8 and 1:1024. The samples with specific fluorescence visible in a 1:16 or higher dilution were considered as *Toxoplasma*-positive. With the help of the personnel of obstetrics clinics, 1038 questionnaires were sent to 1014 women (12 women gave birth to twins). One hundred and ninety-seven (197) of the women were *Toxoplasma*-positive. Only 351 questionnaires (33.8%) were returned back. The respondents included 54 *Toxoplasma*-positive women and 20 subjects who gave birth to twins (10 women). None of the women who gave birth to twins was *Toxoplasma*-positive. Because some of the returned questionnaires were not filled out completely, the number of the assessed women varied between analyses.

To avoid possible fear of women of congenital toxoplasmosis in their children, only general information concerning the purpose of the study was given in the informed consent, namely, the study of the influence of (unspecified) biological and social factors on the development of children. The study was approved by the Institutional Review Board of the Charles University, Faculty of Science and complied with the current laws of the Czech Republic.

2.2. Questionnaire

The questionnaire was designed to collect the following data: the child's birth weight and height, the child's weight and height at the 6th week, 3rd month, 6th month, 12th month, and 18th month of age (as indicated by health care professionals in the childhood immunization record card), breastfeeding duration, age (in months) from which the child was able to control his/her head (was able to lift his/her head up), age at which the child turned over from supine to prone position on his/her own for the first time, and age from which the child was able to sit, crawl, and walk on his/her own. Furthermore, mothers were asked whether they were attending out-patient physiotherapy with the child or were doing some home physiotherapy exercises with the child based on the pediatrician's recommendation.

2.3. Statistical analysis

The Statistika® 8.0 software was used for most statistical testing except the Receiver Operating Characteristic (ROC) curve analysis, which was performed with SPSS 18.0. Twelve women gave birth to twins and their data were excluded from the data set. The influence of latent toxoplasmosis on both returning the completed questionnaire and adhering to out-patient or home physiotherapy was evaluated using the contingency table method.

At first, a general linear model (GLM) for repeated measures was used to evaluate the influence of maternal toxoplasmosis on the child's growth, namely on the weight and the height until 18 months of age. Dependent variables (repeated measures) were the child's weight (or height) at different ages and independent variables in the model were the binary variables toxoplasmosis (negative/positive) and sex of the child. Subsequently, the dependent variables (the child's weight or height at a particular age) were evaluated each separately by using univariate GLM.

The influence of latent toxoplasmosis on the motor development of children was first evaluated using GLM repeated measure test (dependent variables, i.e. repeated measures, child's age from which he/she was able, on his/her own: 1) to control his/her head, 2) to turn over from supine to prone position, 3) to sit 4) to crawl, and 5) to walk). Subsequently, the dependent variables were also evaluated separately by using univariate GLM. The independent variables in the GLM repeated measures and GLM univariate tests were two binary variables: the toxoplasmosis status of the mother and the sex of the child. An attempt to identify a small subpopulation of individuals with developmental disorders among infants of *Toxoplasma*-positive mothers was made only by visual inspection of the ROC curve, as the formal Area under curve test for half-split data was not possible to perform because of the low number of infants of *Toxoplasma*-infected mothers.

3. Results

3.1. Questionnaire response rates in Toxoplasma-positive and Toxoplasma-negative mothers

The results showed that *Toxoplasma*-positive mothers returned the questionnaire marginally less frequently than *Toxoplasma*-negative mothers ($\chi^2 = 3.663$, df = 1, $p = 0.056$). The questionnaire was sent to 197 *Toxoplasma*-positive and 817 *Toxoplasma*-negative mothers and was returned by 53 *Toxoplasma*-positive (26.9%) and 278 *Toxoplasma*-negative mothers (34%). The separate tests for mothers who gave birth to a boy or a girl showed that the effect of toxoplasmosis was significant for 517 women who gave birth to a boy ($\chi^2 = 4.275$, df = 1, $p = 0.039$); of 106 *Toxoplasma*-positive mothers, only 30 (28.3%) returned the questionnaire while of 411 *Toxoplasma*-negative mothers, 161 (39.2%) did so. For 410 women who gave birth to a girl, this effect was not significant ($\chi^2 = 0.188$, df = 1, $p = 0.664$); of 72 *Toxoplasma*-positive mothers, 23 (31.9%) returned the questionnaire while of 338 *Toxoplasma*-negative mothers, 117 (34.6%) did so.

3.2. Association between maternal toxoplasmosis and the child's physiotherapy

The statistical analysis also showed that mothers with latent toxoplasmosis adhered to the home physiotherapy exercises program recommended by the pediatrician less frequently than *Toxoplasma*-negative mothers (n = 322, $\chi^2 = 5.692$, df = 1, p = 0.017): of 52 *Toxoplasma*-positive mothers, only 6 (11.5%) adhered to the home physiotherapy exercises program, while of 270 *Toxoplasma*-negative mothers, 70 (25.9%) adhered to the exercises program. Most mothers were doing the Vojta physiotherapy exercises (Vojta 1993) with the child, with only 2 mothers reporting swimming physiotherapy and physical therapy exercises for hip dysplasia. However, the out-patient physiotherapy attendance rates did not significantly differ between *Toxoplasma*-positive (9.6%) and *Toxoplasma*-negative (18.1%) mothers (n = 322, $\chi^2 = 2.549$, df = 1, p = 0.110).

3.3. Association between maternal toxoplasmosis and infant bioparameters from birth to 18 months

Toxoplasmosis had no effect on the child's birth weight and height: birth weight (n = 331, F = 0.12, p = 0.734; *Toxoplasma*-positive: 3514 g vs. *Toxoplasma*-negative: 3494 g) and birth height (n = 257, F = 0.18, p = 0.668; *Toxoplasma*-positive: 50.9 cm vs. *Toxoplasma*-negative: 50.7 cm). This analysis showed a significant effect of the sex of the newborn, as boys were 200 g heavier on average (F = 8.30, p = 0.004; boys: 3579 g vs. girls: 3385 g) and about 1 cm taller than girls (F = 8.98, p = 0.003; boys: 51.1 cm vs. girls: 50.3 cm). The effect of the interaction of toxoplasmosis and sex of the newborn on the birth weight and height was not significant (weight: F<0.001, p = 1.00; *Toxoplasma*-positive boys: 3599 g, *Toxoplasma*-negative boys: 3576 g, *Toxoplasma*-positive girls: 3404 g, *Toxoplasma*-negative girls: 3381 g, and height: F = 0.27, p = 0.604; *Toxoplasma*-positive boys: 54.4 cm, *Toxoplasma*-negative boys: 51.1 cm, *Toxoplasma*-positive girls: 50.2 cm, *Toxoplasma*-negative girls: 50.3 cm).

GLM with repeated measures was used for the analysis of the infant's growth from 6 weeks to 1.5 years of age, with the weight (or height) at the age of 6 weeks, 3 months, 6 months, 1 year and 1.5 years as independent variables. Infants of mothers with latent toxoplasmosis had a higher weight than those of *Toxoplasma*-negative mothers (n = 248, F = 4.86, p = 0.028), the effect of the sex of the child was also significant (F = 23.80, p<0.001), but the interaction of toxoplasmosis and sex had no effect (F = 0.14, p = 0.707). Neither toxoplasmosis (F = 2.26, p = 0.134) nor toxoplasmosis–sex interaction (F = 0.02, p = 0.880) had any effect on the infant's height; however, the trend toward taller infants for *Toxoplasma*-positive mothers was still present. The male children were significantly taller than female children (n = 190, F = 12.52, p<0.001). Weight or height at particular times were further evaluated separately (Tables 1 and 2); however, the univariate analyses showed no significant differences.

3.4. Association between maternal toxoplasmosis and the child's motor development rate during the first 18 months of life

The results showed that infants of *Toxoplasma*-positive mothers had lower rates of motor development from birth to 1 year of age than infants of *Toxoplasma*-negative mothers (GLM with the time when the child started holding up the head, turning from supine to prone position, sitting, crawling, and walking as repeated measures: n = 217, F = 4.238, p = 0.041). The significance of the GLM repeated measure test highly increased (n = 227, F = 7.7, p = 0.006) when the time of starting to walk was removed from the model. The individual dependent variables were further evaluated separately. In comparison with infants of *Toxoplasma*-negative mothers, the infants of *Toxoplasma*-positive mothers developed the ability to control the head significantly later (n = 262, p = 0.039, *Toxoplasma*-positive: 2.62 months vs. *Toxoplasma*-negative: 2.29 months; effect of the sex: p = 0.006 ; effect of the interaction of toxoplasmosis and sex: p = 0.014), started being able to turn from supine to prone position later (n = 269, p = 0.022, *Toxoplasma*-positive: 4.92 months vs. *Toxoplasma*-negative: 4.48 months; effect of the sex: p = 0.435 ; effect of the interaction of toxoplasmosis and sex: p = 0.251), and were slightly later to begin crawling (n = 293, p = 0.059, *Toxoplasma*-positive: 7.44 months vs. *Toxoplasma*-negative: 7.25 months; effect of the sex: p = 0.132 ; effect of the interaction of toxoplasmosis and sex: p = 0.787) (Fig. 1). Latent toxoplasmosis had no effect on the time when the infant started to sit (n = 298, p = 0.401, *Toxoplasma*-positive: 7.44 months vs. *Toxoplasma*-negative: 7.25 months; effect of the sex: p = 0.713; effect of the interaction of toxoplasmosis and sex: p = 0.954) and to walk (n = 304, p = 0.717, *Toxoplasma*-positive: 11.98 months vs. *Toxoplasma*-negative: 12.11 months; effect of the sex: p = 0.987 ; effect of the interaction of toxoplasmosis and sex: p = 0.451).

GLM with the time when the child started to control the head, to turn from supine to prone position, to sit, to crawl, and to walk as repeated measures and three independent binary variables (toxoplasmosis, sex and home physiotherapy adherence) showed qualitatively the same results as the corresponding analyses with only two independent variables, namely the infants of *Toxoplasma*-positive mothers had lower rates of motor development (n = 216, F = 8.6, p = 0.004) than children of *Toxoplasma*-negative mothers.

It was suggested earlier that women with latent toxoplasmosis have a relaxed stringency of embryo quality control which may result in a higher proportion of infants with genetic or developmental disorders in their offspring. If the delayed postnatal development of children of *Toxoplasma*-positive women were caused by the presence of a subpopulation of infants with developmental disorders among those born to *Toxoplasma*-positive mothers, the ROC curve would decline from the theoretical line

Table 1
Weights of children of *Toxoplasma*-negative and *Toxoplasma*-positive mothers. The first part of the table shows results (significance, p and effect size, η^2) of the univariate GLM analyses with the binary variables maternal toxoplasmosis status and sex of the child as independent variables and weight of the child at a particular age as dependent variables. The significant results are printed in bold, 0.001 indicates significance equal to or lower than 0.001. The second part of the table shows descriptive statistics of the data, the weight is given in kg.

	6 weeks		3 months		6 months		1 year		1.5 years	
	p	Eta^2	p	Eta^2	p	Eta^2	p	Eta^2	p	Eta^2
Toxo	0.787	<0.01	0.246	<0.01	0.102	0.01	0.108	0.01	**0.036**	0.02
Sex	<0.001	0.05	<0.001	0.08	<0.001	0.06	<0.001	0.06	<0.001	0.08
Toxo × sex	0.661	<0.01	0.805	<0.01	0.816	<0.01	0.713	<0.01	0.446	<0.01
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Toxo pozit. girls	22	4.52	22	5.88	22	7.63	21	9.75	18	11.21
Toxo negat. girls	110	4.33	111	5.72	108	7.36	106	9.41	98	10.92
Toxo pozit. boys	25	4.94	27	6.42	27	8.21	28	10.40	23	12.42
Toxo negat. boys	141	4.87	144	6.32	141	8.01	138	10.18	119	11.79

Table 2
Heights of children of *Toxoplasma*-negative and *Toxoplasma*-positive mothers. The first part of the table shows results (significance, p and effect size, η^2) of the univariate GLM analyses with the binary variables maternal toxoplasmosis status and sex of the child as independent variables and height of the child at a particular age as dependent variables. The significant results are printed in bold, 0.001 indicates significance equal to or lower than 0.001. The second part of the table shows descriptive statistics of the data, the height is given in cm.

	6 weeks		3 months		6 months		1 year		1.5 years	
	p	Eta^2	p	Eta^2	p	Eta^2	p	Eta^2	p	Eta^2
Toxo	0.924	<0.01	0.601	<0.01	0.197	0.01	0.209	0.01	0.170	0.01
Sex	0.071	0.01	<0.001	0.09	0.010	0.03	<0.001	0.05	<0.001	0.05
Toxo × sex	0.754	<0.01	0.265	<0.01	0.288	<0.01	0.937	<0.01	0.964	<0.01
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
Toxo pozit. girls	21	55.36	20	60.15	20	68.30	21	75.52	18	82.58
Toxo negat. girls	90	55.58	96	60.46	96	66.95	104	74.85	97	81.72
Toxo pozit. boys	21	56.50	23	63.30	25	69.18	26	77.83	23	84.65
Toxo negat. boys	110	56.38	118	62.44	114	69.05	128	77.06	115	83.85

only in the right part of the ROC graph. The visual inspection of the ROC curves, however, showed that the developmental differences between infants of *Toxoplasma*-positive and *Toxoplasma*-negative subjects can be seen in the whole graph, i.e. even in the infants with above-average rates of motor development, see Fig. 2.

4. Discussion

Our results showed that children of mothers with latent toxoplasmosis expressed lower rates of postnatal development in the first 18 months of life. The infants of *Toxoplasma*-positive mothers later developed the ability to control the head and to turn from supine to prone position and were slightly later to begin crawling. They also had a higher weight than infants of *Toxoplasma*-negative mothers. Mothers with latent toxoplasmosis failed to adhere to the home physiotherapy program significantly more often than *Toxoplasma*-negative mothers. Also, *Toxoplasma*-positive mothers (especially those with male offspring) returned the questionnaire marginally less frequently than *Toxoplasma*-negative mothers.

It could be speculated that lower rates of postnatal development in infants of *Toxoplasma*-positive mothers might result from sex differences in the rates of early postnatal development and from the higher frequency of male infants born to *Toxoplasma*-positive women [10,11]. However, the results showed that *Toxoplasma*-positive mothers who gave birth to a boy returned the questionnaire less frequently than *Toxoplasma*-positive mothers who gave birth to a girl. The lower questionnaire return rate from mothers of boys compensated the higher frequency of boys in the offspring of *Toxoplasma* infected mothers, which resulted in approximately the same number of records for boys and girls in our final set. Moreover, we included the sex of the infant as an independent variable in all statistical tests, and thus we controlled for the possible influence of this factor on the observed effects.

The immunological hypothesis of a *Toxoplasma*-induced sex ratio shift that was recently supported by the immunosuppression observed in *Toxoplasma*-infected mice [12] and humans [15] suggests that *Toxoplasma* (by inducing immunosuppression) rescues many male fetuses with developmental disorders. Generally, the female fetuses with mild disorders have higher chances to survive, which often results in higher sex ratios of aborted embryos observed in spontaneous abortion studies [16]. A significant deviation from a 1:1 sex ratio was reported for a number of chromosome abnormalities [17,18]. For example the sex ratio in spontaneously aborted trisomic embryos was significantly higher than 1.0 [19]. At the same time, a large excess of females was observed among trisomy 18 live borns despite the

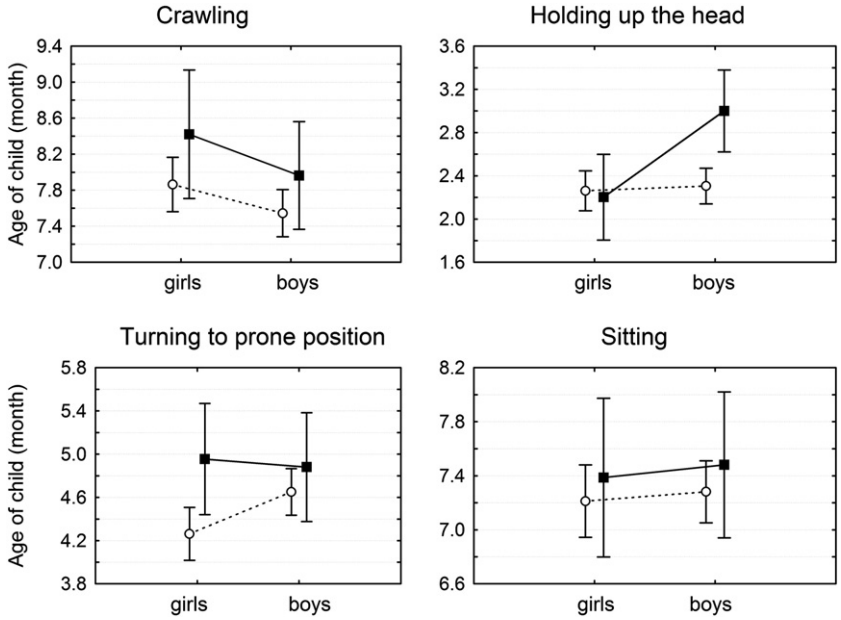

Fig. 1. Differences in motor development rate between girls and boys of *Toxoplasma*-positive and *Toxoplasma*-negative mothers. The y axis shows the mean age (in months) at which the particular subpopulation of children developed the ability to control the head, to turn from supine to prone position, to sit, and to crawl. The circles show the data for children of *Toxoplasma*-negative mothers, the full squares show the data for children of *Toxoplasma*-positive mothers.

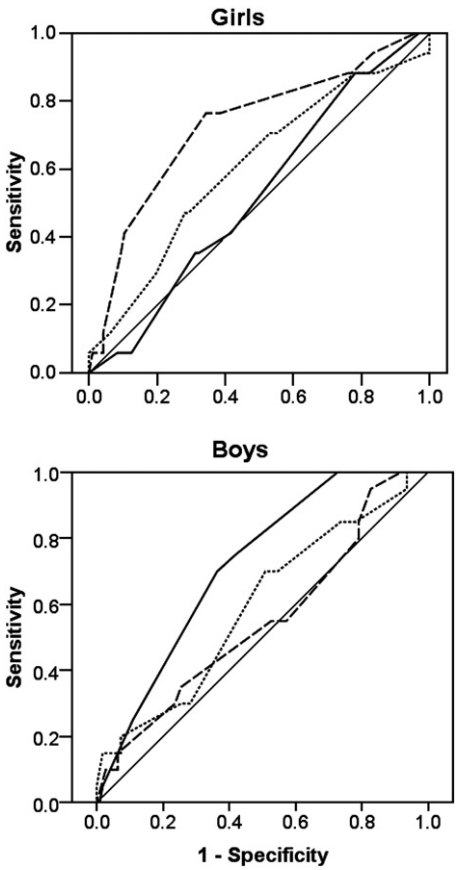

Fig. 2. The area under curve plots showing the discrimination performance between children of *Toxoplasma*-positive and *Toxoplasma*-negative mothers based on their motor development. The receiver operating characteristic curves (ROCs) plot the true positives (sensitivity) vs. false positives (1 — specificity), for a binary classifier system as its discrimination threshold is varied (thin diagonals). The thick lines show the curves (lines) for the classification based on random variable. The size of the area between the diagonals and thick curves reflects the quality of the classification function and therefore also the strength of the relation between the dependent and independent variables. The present two plots (girls vs. boys) show that the relation between the maternal toxoplasmosis status and motor development of the child is significant for controlling the head (solid line, boys: p = .001, girls: p = .814), and turning from supine to prone position (hatched line, boys: p = .674, girls: p = .012), crawling (dotted line, boys: p = .384, girls: p = .137). It is evident that whenever the motor development-based classification performs better than random classification, it performs better also for the left parts of the plots (for children with a better-than-average development rate). Therefore, the visual inspection of the plots does not suggest that a subpopulation of children with developmental disorders among children of *Toxoplasma*-positive mothers is responsible for the observed difference between the mean rates of motor development of children of *Toxoplasma*-positive and *Toxoplasma*-negative mothers.

virtually identical numbers of Y- and X-bearing 18 disomic sperm in men [20].

We suppose that the low return rate of questionnaires from the *Toxoplasma*-positive mothers who gave birth to a boy may have been caused by a higher frequency of boys with various genetic or developmental disorders. It is reasonable to expect that mothers of such children had neither the will nor time to complete and send us the questionnaire. The sieve effect can also explain our failure to identify a subpopulation of children with developmental defects among children of *Toxoplasma*-infected mothers based on the analysis of the ROC curves.

The slower early postnatal motor development of infants of mothers with latent toxoplasmosis might also be a result of the fact that mothers with latent toxoplasmosis adhered to the home physiotherapy exercises program significantly less frequently than *Toxoplasma*-negative mothers. This can be explained by differences in the personality profile between *Toxoplasma*-positive and *Toxoplasma*-negative women. The *Toxoplasma*-positive women are more easy-going and have lower self-discipline — they score higher on Cattell's factor A [2] and lower on Big Five factor conscientiousness [21] than *Toxoplasma*-negative controls. It was shown that regular exercise with children under 1 year had a positive effect on their motor development [22]. However, our analyses provided nearly identical results when the binary variable home physiotherapy yes/no was added to the model. Therefore, our results rather suggest that the differences in the behavior of *Toxoplasma*-positive and *Toxoplasma*-negative mothers (resulting in poorer adherence to home physiotherapy) were not responsible for the slower development of infants of *Toxoplasma*-positive mothers.

The results of this study correspond to the previous findings of lower fetal development rates in mothers with latent toxoplasmosis in comparison with *Toxoplasma*-negative mothers [8,9]. Our results are compatible with the hypothesis that the differences in both the prenatal and postnatal development rates between children of *Toxoplasma*-positive and *Toxoplasma*-negative mothers are caused by a relaxed filtering stringency of embryo quality control [23] in *Toxoplasma*-positive mothers resulting in a higher proportion of infants with genetic or developmental disorders, i.e. of infants with a decreased rate of early prenatal development, in the offspring of *Toxoplasma*-positive mothers.

The increased weight in children of *Toxoplasma*-positive mothers could also be the result of different behavior of *Toxoplasma*-positive mothers [3,21], who possibly due to their different psychological profiles, lower self discipline measured by Cattell's 16 PF [2] and Big Five [21], and lower novelty seeking measured by Cloninger's TCI [24,25] provide less stimuli to their children, which can influence negatively physical activity and therefore positively the weight of children.

4.1. Limitations of the present study

The information obtained using the questionnaire is subjective and is certainly less reliable than that, for example, from medical records. The psychological profile of infected women differs from that of *Toxoplasma*-negative women [2,3,21,26]. It is therefore possible that *Toxoplasma*-positive and *Toxoplasma*-negative mothers perceive and describe an identical motor development of their children differently. It should be reminded, however, that the difference in the postnatal development rates between children of *Toxoplasma*-positive and *Toxoplasma*-negative mothers was also supported by the objective data such as the weight of children that is measured by medical personnel during regular periodic visits of mothers and children to pediatric clinics and is recorded on the child's medical card. It is also important that the slower postnatal development of children of *Toxoplasma*-positive mothers is in agreement with their slower prenatal development as well as with the prior hypothesis that was suggested to explain unrelated data (shift in the sex ratio and an increased probability of giving birth to a child with Down syndrome in *Toxoplasma*-positive mothers).

A major limitation of the present study was the absence of data from the *Toxoplasma*-positive women who decided not to complete and return the questionnaire. The difference in the return rates between *Toxoplasma*-positive and *Toxoplasma*-negative mothers (all mothers: 27% vs. 34%, mothers of boys: 28% vs. 39%) is relatively high and can result in a strong sieve effect. We suppose that mothers of children with developmental disorders are generally busier and less willing to share the data on the development of their children than mothers of healthy children. If it is true, the sieve effect can result in the underestimation of the strength of the observed effect. Theoretically, the mothers of children with developmental defects could be more willing to complete and return us the questionnaire because they pay more attention to the development of their children. If it were so, however, we should expect a higher and not a lower return rate of questionnaires from mothers of children with slower postnatal development, i.e. from the *Toxoplasma*-positive

mothers. Therefore, it would be important to confirm our preliminary results in the future, preferably by a prospective study.

Another potential limitation of the present study was a relatively low number of children in certain subgroups in certain analyses, for example in the analysis of a possible relation between latent toxoplasmosis and adherence to exercising with infants at home. This study needs to be repeated on a larger population of mothers, preferably in a country where screening for toxoplasmosis during pregnancy is mandatory.

Finally, the extensive genetic heterogeneity of *T. gondii* strains must be remembered. Current data show that the strains of this parasite could dramatically differ in their impact on physiology, health and also behavior of infected host [27–29]. In the future studies, it would be desirable to perform serological or even genetic typing of *T. gondii* strains infecting particular females.

Conflict of interest

Neither of the authors have any conflicts of interest to disclose.

Acknowledgments

The research was supported by the Charles University, project UNCE 204004.

References

[1] Havlíček J, Gašová Z, Smith AP, Zvára KJ, Flegr J. Decrease of psychomotor performance in subjects with latent 'asymptomatic' toxoplasmosis. Parasitology 2001;122:515–20.
[2] Flegr J, Zítková S, Kodym P, Frynta D. Induction of changes in human behaviour by the parasitic protozoan *Toxoplasma gondii*. Parasitology 1996;133:49–54.
[3] Lindová J, Novotná M, Havlíček J, Jozífková E, Skallová A, Kolbeková P, et al. Gender differences in behavioural changes induced by latent toxoplasmosis. Int J Parasitol 2006;36:1485–92.
[4] Tenter AM, Heckeroth AR, Weiss LM. *Toxoplasma gondii*: from animals to humans. Int J Parasitol 2000;30:1217–58.
[5] Kimball AC, Kean BH, Fuchs F. The role of toxoplasmosis in abortion. Am J Obstet Gynecol 1971;111(2):219–26.
[6] Giorgino FL, Mega M. Toxoplasmosis and habitual abortion. Our expedice. Clin Exp Obstet Gynecol 1981;8:132–4.
[7] Quablan HS, Jumaian N, Abu-Salem A, Hamadelil FY, Mashagbeh M, Abdel-Ghani F. Toxoplasmosis and habitual abortion. J Obstet Gynaecol 2002;22(3):296–8.
[8] Flegr J, Hrdá Š, Kodym P. Influence of latent toxoplasmosis on human health. Folia Parasitol 2005;52:199–204.
[9] Kaňková Š, Flegr J. Longer pregnancy and slower fetal development in women with latent "asymptomatic" toxoplasmosis. BMC Infect Dis 2007;7:114.
[10] Kaňková Š, Šulc J, Nouzová K, Fajfrlík K, Frynta D, Flegr J. Women infected with parasite *Toxoplasma* have more sons. Naturwissenschaften 2007;94:122–7.
[11] Kaňková Š, Kodym P, Frynta D, Vavřinová R, Kuběna A, Flegr J. Influence of latent toxoplasmosis on the secondary sex ratio in mice. Parasitology 2007;134: 1709–17.
[12] Kaňková Š, Holáň V, Zajícová A, Kodym P, Flegr J. Modulation of immunity in mice with latent toxoplasmosis — the experimental support for the immunosuppression hypothesis of *Toxoplasma*-induced changes in reproduction of mice and humans. Parasitol Res 2010;107:1421–7.
[13] Krackow S. The developmental asynchrony hypothesis for sex ratio manipulation. J Theor Biol 1995;176:273–80.
[14] Hostomská L, Jírovec O, Horáčková M, Hrubcová M. Účast toxoplasmické infekce matky při vniku mongoloidismu dítěte. Česk Pediatr 1957;12:713–23.
[15] Flegr J, Stříz I. Potential immunomodulatory effects of latent toxoplasmosis in humans. BMC Infect Dis 2011;11:274.
[16] Kellokumpu-Lehtinen P, Pelliniemi LJ. Sex ratio of human conceptuses. Obstet Gynecol 1984;64(2):220–2.
[17] Huether C. Epidemiologic aspects of Down syndrome: sex ratio, incidence, and recent impact of prenatal diagnosis. Issues Rev Teratom 1990;5:283–316.
[18] Huether C, Martin R, Stoppelman S, D'Souza S, Bishop J, Torfs C, et al. Sex ratios in fetal and livebirth autosomal aneuploidies. Am J Hum Genet 1996;63:382–90.
[19] Hassol T, Quillen SD, Yamane JA. Sex ratio in spontaneous abortion. Ann Hum Genet 1983;47:39–47.
[20] Griffin DK, Abruzzo MA, Millie EA, Feingold E, Hassold TJ. Sex ratio in normal and disomic sperm: evidence that the extra chromosome 21 preferentially segregates with the Y chromosome. Am J Hum Genet 1996;59:1108–13.
[21] Lindová J, Kuběna AA, Šturcová H, Křivohlavá R, Novotná M, Rubešová A, et al. Pattern of money allocation in experimental games supports the stress hypothesis of gender differences in *Toxoplasma gondii*-induced behavioural changes. Folia Parasitol 2010;57:136–42.
[22] Vojta V. Mozkové hybné poruchy v kojeneckém věku: včasná diagnóza a terapie. 1. české vyd. podle 5. německého. Praha: Grada; 1993. p. 367.
[23] Neuhäuser M, Krackow S. Adaptive-filtering of trisomy 21: risk of Down syndrome depends on family size and age of previous child. Naturwisseschaften 2007;94:117–21.
[24] Flegr J, Preiss M, Klose J, Havlíček J, Vitáková M, Kodym P. Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite *Toxoplasma gondii*. Dopamine, a missing link between schizophrenia and toxoplasmosis. Biol Psychol 2003;63:253–68.
[25] Skallová A, Novotná M, Kolbeková P, Gasová Z, Veselý V, Čechovská M, et al. Decreased level of novelty seeking in blood donors infected with *Toxoplasma*. Neuro Endocrinol Lett 2005;26:480–6.
[26] Flegr J, Havlíček J. Changes in personality profile of young women with latent toxoplasmosis. Folia Parasitol 1999;46:22–8.
[27] Morisset S, Peyron F, Lobry JR, Garweg J, Ferrandiz J, Musset K, et al. Serotyping of *Toxoplasma gondii*: striking homogeneous pattern between symptomatic and asymptomatic infections within Europe and South America. Microbes Infect 2008;10:742–7.
[28] McLeod R, Boyer KM, Lee D, Mui E, Wroblewski K, Harrison T, et al. Prematurity and severity are associated with *Toxoplasma gondii* alleles. (NCCCTS, 1981–2009)Clin Infect Dis 2012;54:1595–605.
[29] Kannan G, Moldovan K, Xiao JC, Yolken RH, Jones-Brando L, Pletnikov MV. *Toxoplasma gondii* strain-dependent effects on mouse behaviour. Folia Parasitol 2010;57:151–5.