Eur J Clin Microbiol Infect Dis (2016) 35:1079–1088
DOI 10.1007/s10096-016-2656-2

REVIEW

Is *Toxoplasma gondii* type related to clinical outcome in human congenital infection? Systematic and critical review

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Received: 24 February 2016 / Accepted: 19 April 2016 / Published online: 4 May 2016

Abstract In human congenital toxoplasmosis the effects of parasite burden and pregnancy time at infection on clinical outcome are well known, but there is controversy regarding the role of *Toxoplasma gondii* type. Through a systematic review of the literature, we aimed to discern if *T. gondii* type has a role on clinical outcome in human congenital toxoplasmosis. We built up a database of congenital toxoplasmosis from reports of cases, case series and screening-based cohorts, which had information about parasite type, gestation time at maternal infection and/or clinical outcome in the product. Then, we obtained frequencies for loci used to genotype geographical origin of cases and types found. Also, odds ratios were calculated for association between time of maternal infection or parasite type on outcome. Type II parasites were the most common in Europe, Asia and Africa, while in America there were mainly atypical strains. More newborns with clinical problems were born from mothers infected during the first half of gestation than from those acquiring the parasite after week 24, regardless of parasite genotype (92.9 vs. 16.1 %, OR = 67.9, CI_{95} 25.4–181.6). Type I and atypical parasites were associated with clinical problems as opposed to types II and III, regardless of pregnancy period at infection (86.9 vs. 72.9 %, OR = 2.47, CI_{95} 1.1–5.4). A significant and remarkable tendency of type I parasites to be present during early pregnancy was also observed (94.4 vs. 5.6 %, $P < 0.009$). In addition to parasite burden and period of gestation, *T. gondii* genotype seems involved in CT clinical outcome.

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Introduction

Toxoplasma gondii is one of the most common parasites worldwide, since it is an obligate microorganism that infects all homoeothermic animals [1]. This pathogen was originally found as a clonal population derived in three lineages (I, II and III) in Europe and North America [2], whereby those of type I are commonly virulent in mice, with LD_{100} 10 parasites; those of type II of low virulence (LD_{50} 10^3 parasites) in the majority of inbred mouse strains; and type III parasites are usually non-virulent, with $LD_{50} \geq 10^5$ [3, 4]. Genotypes not fitting within the three dominant lineages were classified as "atypical", some of them being virulent in mice at isolation [5, 6].

More recent studies have shown a greater variability [7–10]. One of the main studies on genetic *T. gondii* diversity was based on a collection of 956 isolates obtained from various animal species, and used a combination of genetic markers; this analysis led to 138 different genotypes grouped in 15 haplogroups, which collectively define six major clades, spread out around the world from a small number of ancestors [11–14]. Methods commonly used for molecular characterization of *T. gondii* in epidemiological studies are PCR-RFLP, microsatellite analysis and DNA sequencing [2, 11–13, 15, 16]. *B1*, *SAG1* and *SAG2* loci were the first utilized for this purpose [5, 17, 18]. Later *SAG3*, *GRA6* and *BTUB* genes along with *SAG2* were included and used to analyse *T. gondii* genotype in immunocompromised patients [19]. Then, *c22-8*, *c29-2*, *L358*, *PK1* and *Apico* markers were incorporated into a multiplex nested PCR-RFLP [20]. This technique is useful when small amounts of DNA are available from valuable samples and facilitates understanding of the epidemiology and genetic diversity of the parasite [21]. During recent years, different sets of microsatellites have been utilized for this objective, with the more recent being a

multiplex PCR which includes *TUB2, W35, TgM-A, B18, B17, M33, IV.1, XI.1, M48, M102, N60, N82, AA, N61* and *N83* [15, 22, 23].

Transmission of this protozoan occurs horizontally by ingestion of contaminated meals or water, or vertically from mother to embryo/foetus [1, 24]. Congenital toxoplasmosis (CT) frequency in humans depends on the period at which maternal infection occurs, i.e. if early, vertical transmission is of low probability, but it causes major damage, including abortions and still births. In the last weeks, the rate of transmission increases to nearly 72 %, but the foetal disease is clinically absent or less severe; thus, most neonates with CT are born asymptomatic. However, such infections may cause eye or central nervous system sequels later in life [25]. Besides this gestation period effect and that of the parasite burden, it would be important to determine if the parasite type has an effect on disease severity, because it may impact on clinical management; this topic, nevertheless, is still controversial [2, 17, 26].

In order to determine if there is evidence to support a role of *T. gondii* type on clinical aspects of congenital infection, we performed this systematic review of the literature with meta-analysis and are reporting as well as discussing the results herein.

Material and methods

We performed a systematic review of the literature about human congenital *T. gondii* infection genotyping. Articles were sourced from the following publication databases: Google Scholar, ISIWeb, Lilacs, PuBMed, Science Direct, and Scopus using the Mesh: *Toxoplasma gondii* typing, genotyping, children, pregnant woman, toxoplasmosis, genotype, abortions, humans, and CT. Results of articles were included if they presented data on *T. gondii* genotype of confirmed congenital cases; they may also report gestation time at maternal infection or clinical outcome in the product/newborn.

Information was classified according to (a) the source of cases (prenatal/neonatal screening or case report); (b) the clinical outcome: asymptomatic till year of age, CNS/eye disease (cerebral calcification, hydrocephalus, ventriculomegaly, retinochoroidits, microphthalmy and uveitis), systemic damage (jaundice, hepatomegaly, splenomegaly, pneumonitis, purpure, hepatitis, pleural effusion, septic shock, ascites, hypotrophy) or fatal, i.e. abortion, stillbirth or newborn death; and (c) the time at which maternal infection occurred: only two periods could be clearly defined in order to maximize possibility of data analysis, i.e. first (≤24 weeks) and second (>24 weeks).

Genotypes were grouped in classical (type I, II or III), "atypical" (ToxoDB #8, #11, # 36, #41, #65, #67, #108, #162, #166, #206, #229, Africa 1 and TgCTBrca) and recombinant (I/II or I/III). Those types reported as "non-virulent" presented a (TG)7 microsatellite in the beta-tubulin gene, which corresponds to non-virulent strains for mice; also, due to the geographical location (France) they assumed these cases were due to type II parasites ($n=37$) [27]. Mixed infections, i.e. combination of two different genotypes in the same sample, were also included in this study and labelled as "I,II" or "I,III". Parasite genotypes from Argentina, Crete, Cyprus, France, Mexico and Serbia, from mothers with serological evidence of acute infection, were not included in this study, because congenital infection was not confirmed [22, 28–31]. We considered the studies performed with one or more molecular markers for genotyping by PCR-RFLP of protein coding sequences or microsatellite PCR analysis.

Statistical analysis

A database was built with individual values taken from the papers included, using time at maternal infection and parasite genotype as independent variables and clinical outcome as dependent. To measure risk, odds ratio was used, with a $P \leq 0.05$ for statistical significance. The SPSS 22.0 software was used for these purposes.

Results

Thirty-two articles met the criteria of having hard data on genotype, clinical outcome, and/or gestation time at maternal infection (Table 1). From these papers we could gather 372 individual genotyping data, 61.0 % of which also had information about trimester of gestation at maternal infection, and 67.7 % on clinical outcome; 182 cases had both types of information (48.9 %).

Most *T. gondii* genotyping was performed in maternal samples ($n=217$, 58 %), while the rest was done in foetal/newborn fluids or tissues ($n=70$, 19 %), abortion products or placentas ($n=65$, 17 %) or unidentified samples ($n=20$, 5 %). The majority of cases were from screening programs ($n=224$, 60 %), especially in Europe ($n=172$) and America ($n=35$), while clinical reports were collected mainly from Asia ($n=66$) and Africa ($n=39$).

As it can be seen in Table 1, most cases (297 out of 372) were infected by type I, II or III *T. gondii* classical types, with type II being the most common in CT ($n=246$, 66.1 %), including the "non-virulent" strains reported by Costa et al. in 1997 [27], followed by atypical ($n=60$, 16.1 %) and type I ($n=44$, 11.8 %). Only 1.8 % genotypes were type III and mixed infections were reported in 2.7 % of the cases.

As expected, there were differences among continents (Fig. 1a). Genotypes I and II were reported in America, Europe, Africa and Asia. Atypical variants were present

Table 1 *Toxoplasma gondii* genotypes found in human congenital infections worldwide

Continent	Country	Cases (%Cont/%World)	Genotype	Number	Country frequency (%)	Continent frequency (%)	World frequency (%)	References
Europe	United Kingdom	19 (10.2/5.1)	I	6	31.6	3.2	1.6	Aspinall et al. (2003) [32]
			II	7	36.8	3.7	1.9	
			I,II[a]	6	31.6	3.2	1.6	
	Spain	13 (7.0/3.5)	I	6	46.1	3.2	1.6	Fuentes et al. (2001) [33]
			II	1	7.7	0.5	0.3	
			III	1	7.7	0.5	0.3	
			I or III[b]	5	38.5	2.7	1.3	
	France	137 (73.3/36.8)	I	3	2.2	1.6	0.8	Costa et al. (1997) [27]; Howe et al. (1997) [17]; Ajzenberg et al. (2002) [22]; Cneude et al. (2003) [34]; Gilbert et al. (2008) [35]; Elbez-Rubinstein et al. (2009) [36]; Delhaes et al. (2010) [37]; Kieffer et al. (2011) [38]
			II	124	90.5	66.3	33.3	
			III	2	1.5	1.1	0.5	
			Atypical	8	5.8	4.3	2.2	
	Germany	2 (1.1/0.5)	II	2	100.0	1.1	0.5	Howe et al. (1995) [2]
	Holland	1 (0.5/0.3)	I	1	100.0	0.5	0.3	
	Poland	9 (4.8/2.4)	II	9	100.0	4.8	2.4	Nowakowska et al. (2006) [39]
	Romania	1 (0.5/0.3)	II	1	100.0	0.5	0.3	Costache et al. (2013) [40]
	Serbia	3 (1.6/0.8)	I	1	33.3	0.5	0.3	Djurković-Djaković et al. (2006) [41]; Marković et al. (2014) [29]
			II	2	66.7	1.1	0.5	
	Turkey	2 (1.1/0.5)	Atypical	2	100.0	1.1	0.5	Döşkaya et al. (2013) [9]
	Subtotal	187				100.0	50.3	
Asia	Iran	66 (100.0/17.7)	I	12	18.2	18.2	3.2	Asgari et al. (2013) [42]; Sarkari et al. (2015) [43]
			II	54	81.8	81.8	14.5	
	Subtotal	66				100.0	17.7	
America	United States	17 (24.0/4.6)	I	1	5.9	1.6	0.3	Howe et al. (1995) [2]
			II	13	76.5	20.6	3.5	
			III	3	17.6	4.8	0.8	
	Mexico	3 (4.8/0.8)	I	2	66.7	3.2	0.5	Rico-Torres et al. (2012) [31]
			Atypical	1	33.3	1.6	0.3	
	Colombia	7 (11.1/1.9)	I	6	85.7	9.5	1.6	Gallego et al. (2004); (2006) [44, 45]
			III	1	14.3	1.6	0.3	
	Suriname	2 (3.2/0.5)	Atypical	2	100.0	3.2	0.5	Demar et al. (2007) [46]
	Brazil	34 (54.0/9.1)	I,III[a]	1	2.9	1.6	0.3	Vidigal et al. (2002) [47]; Ferreira et al. (2006); (2011) [7, 48]; Carneiro et al. (2013) [8]; Higa et al. (2014) [10]; Silva et al. (2014) [49]
			Atypical	33	97.1	52.4	8.9	
	Subtotal	63				100.0	16.9	
Africa	Egypt	38 (69.1/10.2)	I	5	13.2	9.2	1.3	Abdel-Hameed et al. (2008) [50]
			II	33	86.8	61.0	8.9	
	Tunisia	16 (30.9/4.6)	I	1	6.2	1.9	0.3	Boughattas et al. (2010); (2011a); (2011b) [51–53]
			I,II & I,III[a]	3	18.8	5.6	0.8	
			Atypical	12	75.0	22.3	3.3	
	Subtotal	54				100.0	14.5	
Oceania	French Polynesia	2 (100.0/0.5)	Atypical	2	100.0	100.0	0.5	Yera et al. (2014) [54]
	Subtotal	2				100.0	0.5	
	Total	372					100.0	

%Cont percent of the continent, *%World* percent of the world

[a] Mixed infections

[b] "or" means types I and III could not be distinguished

mainly in America and Africa, while genotype III was found in America and Europe only. Finally, mixed infections have been found in Africa, Europe, and America.

Genotypes were obtained by PCR-RFLP or microsatellite analysis using different genetic markers and variable number of loci (Fig. 1b). In America, 85.7 % of parasites were typed with three to nine protein-coding genetic markers by PCR-RFLP, while the majority of *T. gondii* genotyping in Europe (67.4 %) and Oceania (100 %, $n=2$) was performed by microsatellite analysis. Furthermore, all variants from Asia and most from Africa (70.4 %) were identified with one coding-gene marker.

In general, type I (77.0 %) and II (44.0 %) variants were detected with one genetic marker (*SAG2* gene), while atypical variants have been mainly classified using up to nine protein-coding genes by PCR-RFLP (58.3 %). Also, type II and atypical variants have been identified by multilocus microsatellite analysis in 45.5 % and 21.6 % of the cases. The most common genetic markers were those coding for surface or invasion/replication-related proteins such as: *SAG2* (99.2 %), *GRA6* (26.4 %), *SAG1* (26.0 %), *SAG3* (25.1 %) and *BTUB* (22.7 %).

Most genotyping has been performed in Europe (50.3 %) with type II parasites being prevalent, especially in France (90.5 %). In Spain, the majority of cases were caused by type I parasites. To a lesser extent, atypical and classical III genotypes have also been identified in this continent (Table 1). Genotype II was more frequent in Iran and Egypt as well. Atypical types were reported in Tunisia and French Polynesia. In America, type II parasites have been found in a large proportion in the United States, while in Colombia and Mexico type I parasites prevail. Those called "atypical"—due

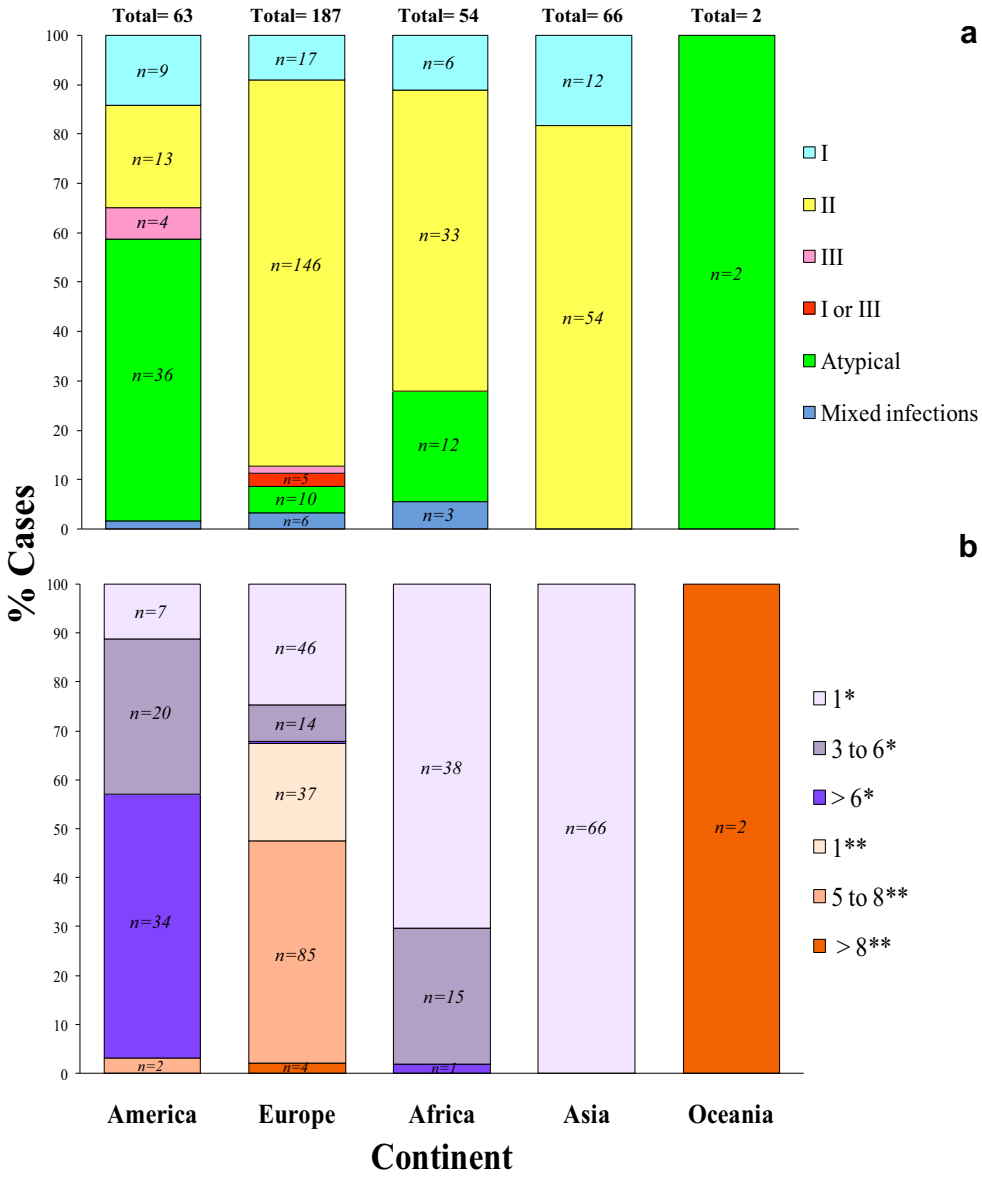

Fig. 1 *Toxoplasma gondii* genotyping in human congenital infections worldwide. **a** Distribution of *T. gondii* parasites by continent. **b** Number of genetic markers used. *PCR-RFLP; **Microsatellite analysis. Atypical genotypes included: ToxoDB #8, #11, # 36, #41, #65, #67, #108, #162, #166, #206, #229, Africa 1,TgCTBrca and recombinant I/II or I/III; Mixed infections were composed of a combination of I,II and I,III types

to the presence of "extra bands" corresponding to "new alleles" in the restriction patterns of *SAG1*, *c22-8*, *BTUB* or *SAG2* loci—have been reported mainly in Brazil and Tunisia, but they have also been found in Mexico (Table 1) [8, 10, 31, 52].

During the first period of gestation, 56.4 % of cases were clinical findings (mainly deaths) and even among those diagnosed by screening the majority were ill or dead (Fig. 2a). The nine asymptomatic cases were due to type II or atypical *T. gondii* variants (Fig. 2c). Conversely, infections of the second half of gestation were mainly detected by prenatal/neonatal screening, most being newborns asymptomatic for up to one year (83.9 %), followed by cases with CNS/eye alterations and two newborns with systemic disease (Fig. 2b and d). Only five cases infected during the second half came from clinical reports, four with fatal outcome and one with CNS/eye disease. As expected and independently on parasite type, most cases infected before the 24th week of pregnancy presented clinical problems (90.8 %), while only 16.1 % of those infected during the second period had bad outcome (Table 2). Remarkable is that all cases infected by type I parasites were symptomatic regardless of time at infection (Fig. 2c and d).

Besides pregnancy time at infection, parasite type (I or atypical) represented a risk for clinical problems in congenitally infected newborns (Table 2). Furthermore, type I parasites had a significant tendency to infect during the first period of gestation in comparison to the second one (Table 3). When type I variants were compared with variants II and III, this tendency increased. Finally, when infections by type I variants were grouped with atypical and compared to types II and III, the risk decreased to 1.7 (Table 3).

Since almost 37 % of the cases included in the present study came from France alone, we performed a more detailed analysis of the data published from this country. Only 88 individual data had parasite genotype, period of gestation at maternal infection and clinical outcome. Similar results to those of the global analysis arose: 77 cases were infected by type II parasites; all those of the first half presented clinical problems ($n = 32$), while only 4.4 % of the second period (2/45) had bad outcome. Moreover, the two type I and the seven atypical cases, presented bad outcome. The only two asymptomatic newborns infected with type III variants (Fig. 2d) were reported in this study.

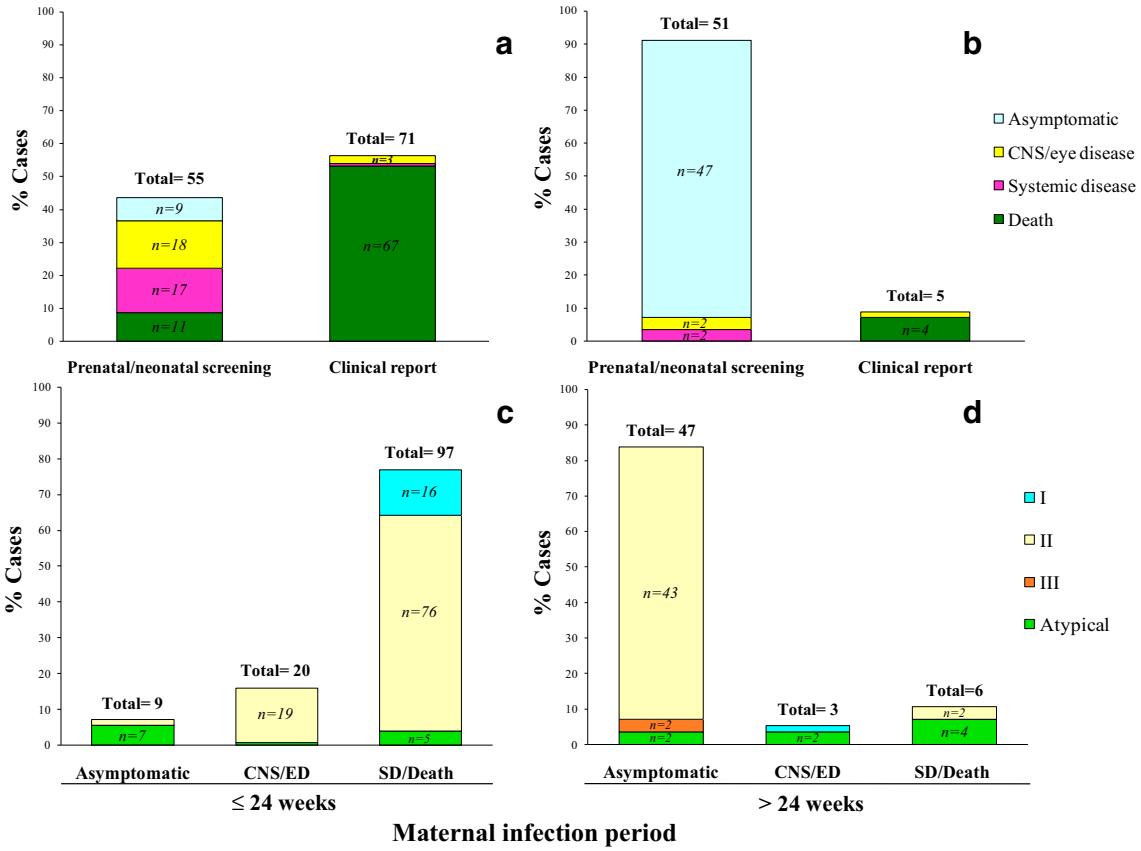

Fig. 2 Relation of clinical outcome in the newborns with period at maternal infection and origin of cases (**a** and **b**) or parasite genotype (**c** and **d**). Asymptomatic = newborns without clinical problems for up to 1 year after birth. CNS/eye disease = cerebral calcification, hydrocephalus, ventriculomegaly, retinochoroidits, microphthalmy, uveitis. Systemic disease = jaundice, hepatomegaly, splenomegaly, pneumonitis, purpure, hepatitis, pleural effusion, septic shock, ascites and hypotrophy. Death = abortion or fetal/newborn death

Table 2 Relation between time at maternal infection or parasite genotype and clinical outcome in newborns with congenital toxoplasmosis

Variable	Total	Clinical problems[a]		Odds ratio (CI $_{95\%}$)	$P \leq 0.05$
		Number of cases	Percent (%)		
Gestation weeks at infection					
≤24	126	117	92.9	67.9 (25.4–181.6)	< 0.0001
>24	56	9	16.1		
Parasite genotype					
I or Atypical	69	60	86.9	2.47 (1.1–5.4)	< 0.012
II or III	181	132	72.9		

[a] Affection of the central nervous system, the eye, the whole body system, some leading to death

Discussion

There has been a controversy regarding the importance of *T. gondii* type on clinical problems developed in the human host; some researchers have claimed there is no clear association between genotype and phenotype [26]. As a matter of fact, most adults with acquired toxoplasmosis are apparently healthy all their lives. But caution must still be taken, since chronic subtle (and not so subtle) alterations have been associated with "subclinical" *T. gondii* infection [55]. The host immune response profile seems important in these cases, with both innate and TH1(/TH17?)-regulated mechanisms involved in protection and clear disadvantage of those individuals who suffer an immune depression, either due to treatment or to infection, for example, with the human immunodeficiency virus [56–61]. Exceptions to this rule seem to be cases of ocular toxoplasmosis in South America, which develop problems in spite of immune competence; it is important to mention that they are caused by atypical *T. gondii* variants [7, 62].

The severity of the congenital disease is influenced by the time of gestation at which the mother became infected, as reported by Dunn et al. in 1999 [25]. So there was no surprise that the meta-analysis reinforced this notion, i.e. there were more cases with clinical problems in newborns of mothers infected during the first half of gestation than in those acquiring the parasitosis in the second part, with a strong and significant risk value. These could be explained by the fact that the foetal immune response is quite immature as compared to that in the newborn [63–65].

Besides pregnancy time at infection, clinical outcome in congenitally infected products depends on parasite burden. Romand et al. (2004) observed that a concentration larger than 100 parasites/mL in amniotic fluid was strongly associated with a severe outcome (OR = 25.1, $CI_{95\%}$ 4.4–143.1), and that these parasite loads were mostly reached if infection occurred in the first half of gestation. Remarkably, the few cases with <100 tachyzoites/mL in early pregnancy were born asymptomatic or with few clinical problems. Moreover, the amniotic fluid of infections acquired after 20 weeks harboured relatively low parasite concentrations and very few cases were born with severe CT. Therefore, gestational age at maternal infection and parasite load in amniotic fluid can be used as early markers for CT severity. Unfortunately they did not type the parasites which infected those cases [66].

Table 3 Relation between time at maternal infection and *T. gondii* genotype in congenital toxoplasmosis

Variable	Total	Genotype		Odds ratio (CI $_{95\%}$)	$P \leq 0.05$
		n (%)	n (%)		
Gestation weeks at infection					
Type		I	II	8.28 (1.1–63.8)	< 0.011
≤24	134	17 (94.4)	117 (67.2)		
>24	58	1 (5.6)	57 (32.8)		
	192	18	174		
Type		I	II or III	8.57 (1.1–66.0)	< 0.009
≤24	134	17 (94.4)	117 (66.5)		
>24	60	1 (5.6)	59 (33.5)		
	194	18	176		
Type		I or atypical	II or III	1.7 (0.8–3.6)	< 0.108
≤24	154	37 (77.1)	117 (66.5)		
>24	70	11 (22.9)	59 (33.5)		
	224	48	176		

A less clear picture exists regarding the role of parasite type and clinical outcome. There is a great variety of *T. gondii* genotypes reported in CT cases around of world. Individual studies have failed to demonstrate either an association with clinical outcome or even a lack of relation. This is why we performed this review, and found evidence that supports this hypothesis. One possible bias that could be argued is that this review included clinical reports, but of the 372 individuals 60 % were detected through screening, in countries both in Europe (mainly France) and America (mainly Brazil) [8, 10, 22, 49, 67, 68]. It is important to mention that we are including literature published in a 20-year period (1995 to 2015), so we are comparing the first genotypes reported on the basis of only one marker—which discerned among three clonal lineages and "atypical" variants—with recent studies, which are based on a larger number of markers and thus allow better differentiation among "atypical" strains, more prevalent in Brazil or French Polynesia, as well as identification of recombinants [49, 54]. Despite this, the geographical distribution emerged in this review is similar to that reported by Su et al. (2012), who reported clonal lineages mainly present in the northern hemisphere and high polymorphism in South America; these data were gathered using samples collected from animals mainly, which are considered sentinels of *T. gondii* infection [14]. This gives support to the findings of the present work, which showed classical strains predominance in Europe-Asia-Africa and atypical genotypes in America-Oceania; especially considering that most cases of Europe (55 %) and America (88.9 %) were characterized with more than three genetic markers.

Although already 20 years have passed from the first *T. gondii* genotype was reported, the role of the parasite type on congenital toxoplasmosis is still controversial [26, 69]. Initially, virulence was defined in laboratory mice with acquired toxoplasmosis on the basis of LD_{50}. Direct assays for the biological basis appeared later; for instance, type I parasites have high rates of multiplication, pathological events induction and crossing of biological barriers in mice [70, 71]. Later, a relation between *T. gondii* type and immune response profile was suggested, virulent strains associated with poorly controlled Th1 response (IFN-γ, TNF-α) [72], which may kill the host by inflammatory processes [73, 74]. Moreover molecules like IFN-γ, MIF or ICAM-1 indirectly may help the parasite to cross through the syncytiotrophoblast, arriving in the foetal blood stream during early stages of gestation [75–77]. Additionally, some type I parasite molecules may allow pathogen growth and host death by excessive parasite burden, such as ROP16 (which induces activation of STAT3/6) and ROP18 (which phosphorylates and inactivates Interferon Regulated GTPases) [78, 79]. Thus, larger numbers of tachyzoites could reach the embryo/foetus and cause damage.

In the present review we observed type I variants were more frequent among infections of the first half of gestation (see Fig. 2c and d) and all cases were clinically severe. In contrast, type II parasites are very effective in activating an early immune response which destroys tachyzoites and induces cyst formation [78, 80]. Those neonatal cases infected by type II strains during the first half of pregnancy presented severe clinical problems (see Fig. 2c), suggesting a crucial role of the immature status of the immune response of the foetus in disease susceptibility. It is important to mention that most of the cases analyzed in this study were monitored until one year of age, so it is not known if asymptomatic babies that were infected during the second period of gestation presented clinical problems later on.

Type III parasites inhibit the early production of pro-inflammatory cytokines and induce cyst formation, leading to chronic infection in humans and animals [80, 81]. Both cases infected by type III *T. gondii* reported herein were asymptomatic and were of the second half of gestation, but they are very few.

According to the present study, atypical parasites gave rise to both asymptomatic and severe CT, regardless of gestation period at infection; these parasites belong to three clades and compose the majority of genotypes worldwide [14]. So, with further classification into subgroups, a large number of cases from other parts of the world are needed to finely understand the relation between these genotypes and clinical outcome in congenital toxoplasmosis.

McLeod et al. performed serotyping of *T. gondii* using the GRA6 and GRA7 polymorphic peptides in a large cohort of cases with CT and found an association between type II parasites and better clinical outcome as compared to those with non-type II infections [82]. Although this study was not included in the datasheet because the article lacked information on pregnancy period at maternal infection, it would support the fact that the parasite type is important for generation of clinical problems in CT. In fact, the present review suggests that type II strains are not aggressive during first year of life unless infection occurs in the first half of gestation. It must be emphasized that there is no prenatal screening program in the United States, thus the results are reflecting what naturally occurs without maternal prophylactic treatment.

In the editorial of the same volume where McLeod et al. published their work, Ajzenberg argues that differences between the United States and Europe (especially France) may arise from the prenatal program established in the latter and not from the parasite type (>90 % of cases are type II in France) [26]. But as stated in the last part of the results section, the observations made for the whole world from the available data can also be gathered by analysis of France alone, i.e. that type II strains are inducing damage if they infect before the 24th week of gestation and not if they get infected later.

This review indicates that besides time of maternal infection, concentration of parasites and maternal/foetal immune response, *T. gondii* type is involved in the severity of congenital toxoplasmosis. In fact we think there is evidence to support these four aspects are related to each other.

If the parasite type is important for disease outcome, it can influence clinical management; especially because there are few therapeutic possibilities and the more efficient regimen nowadays has serious side-effects [83]. The peptide-based serological typing developed some years ago would simplify prognosis, and thus it would improve decision-making about dose therapy and duration [84].

Conclusions

The following conclusions could be gathered from analysis of articles included in the present review:

- Gestation period at maternal infection is critical for the development of foetal damage in the case of infections with *T. gondii* type II.
- Congenital infection due to genotype I parasites is apparently more frequent during the first period of gestation.
- Atypical variants were not associated with clinical outcome, but they compose by far the largest group of *T. gondii*, thus, they deserve further analysis.

Compliance with ethical standards

Funding This work was partially supported by grant 139721 from CONACyT, México.

Conflict of interest The authors declare no conflict of interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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