Toxoplasmosis associated with Down syndrome: A global meta-analytic exploration of elevated infection risk and immune dysfunction

Review Article

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ABSTRACT

Down syndrome (DS) is a genetic condition marked by the presence of an additional copy of chromosome 21, often associated with intellectual disability and other neurologic disorders. Patients with DS exhibit heightened susceptibility to infectious diseases, including toxoplasmosis, attributable to immune dysregulation, and anatomical variations. This systematic review screened existing evidence to evaluate prevalence and the potential association between toxoplasmosis and DS. Following the PRISMA guidelines, an electronic search was conducted across major databases such as PubMed, Web of Science, ScienceDirect, Scopus, EMBASE, and Google Scholar, up to May 2025. The search strategy aimed to identify all relevant studies on *T. gondii* and DS. The pooled prevalence of *T. gondii* seropositivity among DS patients, as well as the pooled odds ratio, was calculated using the random-effects model in StatsDirect software. The present review underscores a significant epidemiological signal warranting heightened clinical awareness.

Keywords: Down syndrome; seroprevalence; toxoplasmosis.

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INTRODUCTION

Down syndrome (DS) is an aberrant chromosomal disease associated with the occurrence of an additional chromosome 21 and occurs in approximately one out of every 750 live births[1]. Of note, DS results in a wide variety of anomalies and disabilities such as abnormalities of digestive and respiratory systems, thymus smallness, specific face appearance, congenital heart defects, and immunodeficiency[2,3]. Some genetic and physical elements collectively cause decreased immune function in DS patients[4]. For instance, there is an imbalance of the quantity and diversity of immune cells, such as T-cells, B-cells, and natural killer cells[5].

These immune cells also play a crucial role in the identification and fighting of infection, and their dysfunction can lead to the compromised ability to mount an effective immune response[5,6]. Furthermore, the thymus gland in DS patients is also smaller and less functional, leading to compromised T-cell production and maturation[7,8]. Additionally, DS patients often have an exaggerated inflammatory response that can also take part in immune dysregulation[9,10]. Besides, DS includes disturbances of the gut microbiota and consequent disturbance of types and quantities of health-promoting bacteria[11]. This intestinal dysbiosis can impact the development and function of the immune system. Accordingly, patients with DS are more susceptible to intestinal dysbiosis impacting the immune system development and performance. A higher vulnerability to a multitude of infections including respiratory infections, ear, and gastrointestinal infections were observed in DS patients[12]. This was attributed to the combination of immune dysfunction, and anatomical differences, such as narrow airways and eustachian tubes[3]. Therefore, the impaired immune system in DS patients makes them susceptible to infections like toxoplasmosis and to a higher risk of autoimmune and inflammatory diseases[9,13]. Understanding the etiology of immune dysfunction in DS is crucial to develop specific interventions and improve overall health outcomes.

On the other hand, *T. gondii* is an intracellular protozoan that is a member of the family Apicomplexa and can infect a large host range of cold-blooded as well as warm-blooded animals[14]. According to figures published by the World Health Organization,

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approximately one-third of the entire world's population are infected with the parasite[15,16]. Infections may be contracted by human beings by eating raw or undercooked meat containing tissue cysts, water or food and vegetables contaminated with oocysts shed in feces of infected cats[17]. Additionally, infections during pregnancy might lead to congenital toxoplasmosis[17,18]. Toxoplasmosis in immunocompetent individuals is normally asymptomatic or may be accompanied by mild fever or cervical lymphadenopathy, while in immunocompromised patients, complications are commonly reported[19-21]. Ocular toxoplasmosis and fatal encephalitis are among toxoplasmosis complications in immunocompromised individuals[22].

Given the increased susceptibility of DS individuals to infections due to immune dysfunction and the pathogenicity of *T. gondii* in immunocompromised patients, the aim of this study is to systematically compile the available evidence to evaluate prevalence and the potential association between the infection and DS.

METHODS

Study design and search strategy: In strict adherence to the PRISMA 2020 statement and guidelines for systematic reviews[23], a comprehensive, reproducible electronic search strategy was meticulously designed and executed to identify all relevant studies investigating the association between *T. gondii* and DS. The search encompassed major international databases (PubMed, Web of Science, Scopus, EMBASE, ScienceDirect, and was supplemented by searches in Google Scholar and scrutiny of relevant clinical trial registries up to May 31, 2025.

Two independent authors (Tork M, and Basirpour B), both experienced in systematic review methodology, developed the search strategy collaboratively. It incorporated a robust combination of controlled vocabulary (Medical Subject Headings (MeSH) in PubMed/EMTREE in EMBASE) and free-text keywords to maximize sensitivity and specificity. Concepts of the core search were:

1. *Toxoplasma* ***gondii:*** (*Toxoplasma gondii* [MeSH] OR *Toxoplasma* [MeSH] OR Toxoplasmosis [MeSH] OR "*Toxoplasma gondii*" OR "*T. gondii*" OR *Toxoplasma* OR toxoplasmosis).
2. **Down Syndrome:** (Down Syndrome [MeSH] OR "Down Syndrome" OR "Down's Syndrome" OR Trisomy 21 OR "Trisomy G" OR "47,XX,+21" OR "47,XY,+21" OR mongolism.

These concept blocks were combined using the Boolean operator AND. Within each block, synonymous terms were combined using OR. Search syntax was meticulously adapted for the specific requirements (field tags, truncation symbols) of each database. The full, reproducible search syntax for at least one major database (*e.g.*, PubMed) is provided in the supplementary material.

All retrieved records underwent a rigorous, two-phase screening process managed using EndNote. First, titles and abstracts were screened independently by MT and BB against predefined eligibility criteria. Second, full texts of potentially relevant articles were obtained and assessed independently by the same reviewers. Any discrepancies at either stage were resolved through discussion; persistent disagreements were judged by a third senior author (Hosseini SA) to reach a final consensus. The review protocol was prospectively registered on PROSPERO prior to commencing the searches.

Inclusion and exclusion criteria: The characteristics of inclusion criteria for our review include: (i) all case reports and retrospective studies relevant to *Toxoplasma* and DS; (ii) relevant articles until October 2024; (iii) English manuscripts; and (iv) human studies. Also, exclusion criteria include: (i) articles for which full texts were not available; (ii) duplicated articles; (iii) presented in congresses; or (iv) were not in English, (v) review and meta-analysis review, letter and note.

Quality assessment: Two independent reviewers, Tork M and Basirpour B, evaluated the quality of the study articles using the Joanna Briggs Institute (JBI) assessment cards[15]. This tool has a checklist consisting of 8 questions (quality of study, clarity, and details), and studies that scored higher than 4 were included in the review.

Data analysis: A meta-analysis was conducted using StatsDirect software, version 2.8.0 (http://statsdirect.com) to calculate the pooled prevalence of toxoplasmosis in DS patients and its 95% confidence interval (CI). Cochrane's Q and the inverse variance (I^2) statistics were used to assess the heterogeneity of the studies. If I^2 was greater than 50% or 75%, the studies were considered heterogeneous or highly heterogeneous, respectively. If I^2 was below 25%, the studies were considered homogeneous. In cases of significant heterogeneity, random-effects models for proportion and odds ratio (OR) were employed to estimate the prevalence of *T. gondii* in DS patients and to examine the potential connection between them. A funnel plot based on Egger's test was used to assess publication bias. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Study characteristics: Our initial search across databases, including PubMed, Web of Science,

ScienceDirect, Scopus, EMBASE, and Google Scholar, yielded 198 articles. However, 99 of these were excluded due to duplication. Figure (1) illustrates the study selection process. After an initial screening of the article titles, 86 studies were retained. In the next phase, 13 articles were excluded after screening the abstracts based on the inclusion and exclusion criteria. Following a review of the full texts, 79 more papers were excluded. Ultimately, 9 articles (7 datasets for meta-analysis and 2 case reports) were included in the meta-analysis, adhering to the specified criteria[24-32]. Moreover, after evaluating the quality of the included studies, the calculated mean score of the studies quality was 6.14±0.5. Table (1) provides the baseline characteristics of the included case-control and cross-sectional studies related to the prevalence of toxoplasmosis in DS patients[24-30]. Additionally, the characteristics of the case report studies are summarized in table (2)[31,32].

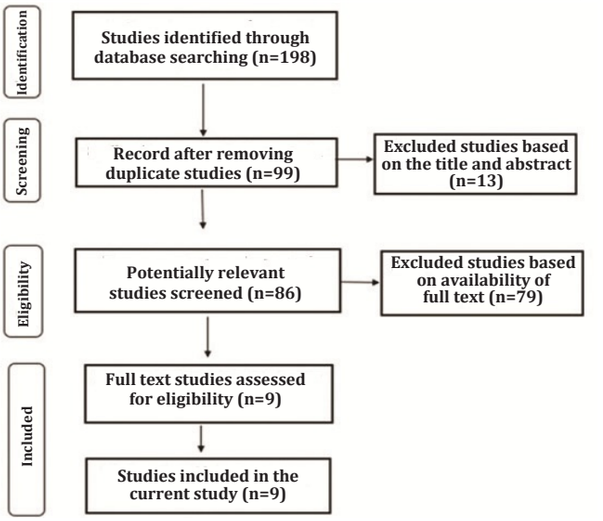

Fig. 1. PRISMA flow chart of study identification and selection.

The pooled seroprevalence of toxoplasmosis in DS patients: The results of the meta-analysis showed that the heterogeneity between the included studies was significant (Q = 97.89, df=6, I2= 93.9%, *P*<0.001). Therefore, the random effect was used to obtain the pooled prevalence of toxoplasmosis among patients with DS (Fig. 2).

Generally, 707 individuals with and without DS were used for meta-analysis. The pooled prevalence of *T. gondii* seropositivity among patients with DS using the random effect method was 24.2% (95% CI = 8% to 44%). Furthermore, based on the funnel plot and bias coefficient diagram (Fig. 3), the included studies had no significant publication bias based on Begg-Mazumadar bias (*P*=0.069).

The association between being a DS patient and toxoplasmosis: The pooled random effect didn't show any statistically significant increased risk of *T. gondii* seropositivity in DS patients compared with individuals with positive mental health (Pooled odds ratio = 1.36, 95% CI: 0.50 to 3.72, I2 = 58.2%, Q = 7.18, *P*=0.0663) (Fig. 4).

Table 1. Baseline data of case-control and cross-sectional studies related to prevalence of toxoplasmosis in DS patients.

Country	Total No.	No.	Case group		No.	Control group		Ref.	Q.A.
			+ve IgG	+ve IgM		+ve IgG	+ve IgM		
			No. (%)	No. (%)		No. (%)	No. (%)		
Russia	194	63	2 (3.17)	-	-	-	-	[24]	4
Brazil	45	24	8 (33.33)	-	21	12 (57.14)	-	[25]	5
Egypt	188	29	10 (34.48)	3 (10.34)	-	-	-	[26]	7
Egypt	60	30	4 (13.33)	1 (3.33)	30	3 (10)	2 (6.66)	[27]	8
Egypt	358	20	18 (90)	2 (10)	203	164 (80.78)	38 (18.71)	[28]	8
Yemen	107	107	3 (2.8)	-	-	-	-	[29]	5
Egypt	180	90	16 (17.77)	-	90	6 (6.66)	-	[30]	6

QA: Quality assessment based on Joanna Briggs Institute (JBI) assessment cards[15].

Table 2. Baseline data of case reports of toxoplasmosis in DS patients.

Country	Gender	Age	Underlying disease	IgG/ IgM	Confirmation of toxoplasmosis	Treatment	Ref.
Japan	New born	2 W	Diabetes	IgG^+/ IgM^+	SAG1 gene was detected from CSF cells by PCR and tachyzoites in CSF sample	Pyrimethamine-sulfadiazine, Atovaquone, Clindamycin	[31]
USA	Female	20 y	lymphocytic leukemia	IgG^+	Tachyzoites in the smear of the pleural fluid	Pyrimethamine, Sulfadoxine, Leucovorin, Prednisolone	[32]

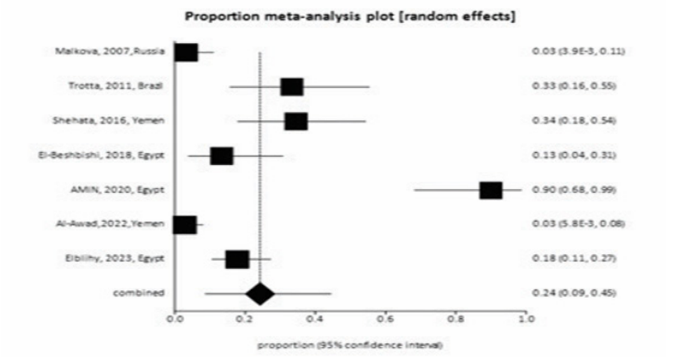

Fig. 2. Forest plot of seroprevalence of toxoplasmosis in DS patients, estimated with random effects model.

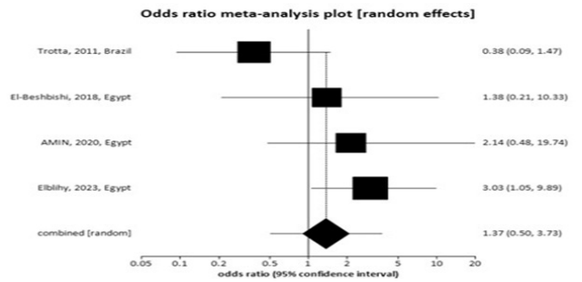

Fig. 4. Forest plot of f the association between toxoplasmosis seropositivity and being a DS patient, estimated with random effects model, showing the OR with 95% CI.

DISCUSSION

The elevated seroprevalence of toxoplasmosis observed in individuals with DS, intensified by their characteristic spectrum of congenital comorbidities and immunodeficiencies, necessitates heightened clinical attention and prompt diagnostic assessment in this population. The DS affection is associated with a complex of clinical phenotypes involving significant developmental delay, intellectual disability, congenital cardiovascular and gastrointestinal anomalies, and inherent immune dysregulation[33]. As a result of these susceptibility factors, individuals with DS are at higher risk for a comprehensive collection of infections. Therefore, a complete understanding of their susceptibility to toxoplasmosis is essential in order to improve their overall well-being and quality of life.

Even though toxoplasmosis in healthy individuals is often asymptomatic or mild, the manifestations of chronic or latent infection may be more apparent in DS individuals[19]. Due to their potentially weakened immune systems and underlying medical illnesses, these patients are at risk of more serious or longer-duration effects from the infection[3,7,11]. Toxoplasmosis exposure screening is particularly crucial in this group, as it can avoid the worsening of cognitive, neurological, or immune status outcomes[3]. Proactive identification of at-risk individuals and implementation of targeted

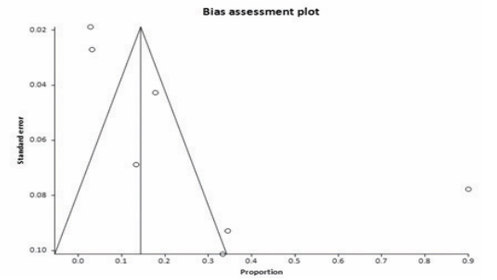

Fig. 3. Publication bias calculated for included studies using funnel plot.

preventive strategies are critical for mitigating the long-term sequelae of toxoplasmosis and optimizing health outcomes and quality of life in individuals with DS.

In addition, studies show that toxoplasmosis is a neurotropic infection with microinvasive traits, potentially having an impact on neurodevelopment as well as behavior[34,35]. Though data in DS is currently limited, the increased incidence of toxoplasmosis in this group warrants studies on its potential impact on neurodevelopment and cognitive processes. Experiments targeting the pathogenic function of toxoplasmosis in DS can explain whether or not this parasite is the cause of increasing the development or behavior disorders characteristic of this population.

Totally, based on systematic searching of various scientific databases regarding inclusion and exclusion criteria, there were 9 included studies that consist of 7 case-control[24-30] and 2 case reports[31-32] in the present review. That the majority of the studies included were case-control studies is a desirable aspect, as this study design allows for the comparison of cases with DS and controls, and can therefore be utilized to establish potential risk factors for toxoplasmosis. The meta-analysis findings indicated that the pooled seroprevalence of toxoplasmosis among DS patients was 24.2%, which was significantly higher compared to the general population. However, there was not a statistically significant increase in the risk of toxoplasmosis in DS patients when compared to the healthy population (Pooled odds ratio = 1.36, 95% CI: 0.50 to 3.72, I^2=58.2%, Q=7.18, *P*=0.0663). A number of methodological constraints could account for the non-significant correlation found, such as diagnostic inconsistency, uneven environmental exposure, divergence in preventive measures, and intricate confounding mechanisms that might conceal a genuine epidemiological association.

Yet, the chronically elevated *T.gondii* seroprevalence in DS patients over controls indicates its clinical significance as a comorbid condition. Knowledge of this association has far-reaching implications because intrinsic immune dysregulation and multisystem comorbidities in DS enhance susceptibility to

opportunistic pathogens such as *T. gondii*. The global seroprevalence of toxoplasmosis is estimated at 10-20%, demonstrating substantial geographic variation attributable to region-specific risk factors[27].

The higher prevalence among DS individuals can be explained by a range of reasons, including impaired immunity status, since DS individuals develop an altered immune response[28]. Immune dysfunction, such as diminished phagocytic ability and a generally impaired ability to mount an effective immune response[5,28,29], may predispose this population to higher rates of parasitic infections, including *T. gondii*[12,30].

Additionally, impaired ability of persons with DS to maintain personal hygiene may enhance the risk for *Toxoplasma* exposure[4,31]. Due to personal care challenges, including hand hygiene and food handling[32], and potential cat contact (the definitive host of *T. gondii*), this population may be at increased risk for infection.

The fact that there are so few studies in general (only 9 studies) is a limitation, particularly because they are geographically limited to a small number of countries: Russia, Brazil, Yemen, and Egypt. This geographic limitation reduces the generalizability of results to other regions. While the two case reports illustrated here are complete descriptions of *T. gondii* presentation in DS, their nature as case reports does limit generalizability to the broader population.

Not withstanding their value in documenting novel presentations or rare complications, case reports lack the statistical power to establish epidemiological patterns or population-level risk factors. Case reports, however, help to reinforce the inclusion of toxoplasmosis as part of clinical management of individuals with DS, particularly in endemic areas where the parasite is extremely common. Case reports have a higher rate of reporting severe or unusual outcomes of toxoplasmosis, and in DS such an infection could aggravate cognitive, neurological, or immune issues. Although the case reports that were outlined in this review were not necessarily proof of a causal relationship between toxoplasmosis and aggravation of symptoms of DS, they indicate that medical practitioners should be more alert for the possible impact of toxoplasmosis on DS patients, particularly those that are at high risk.

Limitations: This systematic review is subject to several notable limitations that warrant consideration when interpreting its findings. Firstly, the synthesis is constrained by the limited number of included studies (n=9), predominantly case-control designs (n=7) with few case reports (n=2), restricting the generalizability of conclusions. Secondly, the geographical scope is narrow, encompassing only studies from Egypt, the USA, Japan, Russia, Yemen, and Brazil. This limits the external validity and applicability of findings to populations with differing epidemiological, socioeconomic, and healthcare contexts. Thirdly, significant methodological heterogeneity was observed among studies, including variations in diagnostic criteria and participant characteristics, complicating data synthesis and potentially biasing pooled estimates. Fourthly, the inherent risk of bias in case-control studies such as selection bias, recall bias, and contradictions (*e.g.*, control group composition not reflecting the general population), threaten internal validity. Fifthly, substantial heterogeneity in *T. gondii* diagnostic methods (*e.g.*, different serological assays and sensitivities) compromises the consistency of seropositivity detection and overall prevalence estimation. Sixthly, the generally small sample sizes across most included studies reduce statistical power and increase the risk of Type II errors. Finally, insufficient control for key contradictory variables (*e.g.*, living conditions, healthcare access, and hygiene practices) may lead to over- or underestimation of the association between toxoplasmosis and DS. Future research employing larger, multi-center cohorts, standardized diagnostics, and rigorous control for confounders is essential to enhance the robustness and generalizability of evidence.

CONCLUDING REMARKS

1. The seroprevalence of toxoplasmosis in individuals with DS is relatively higher than in the general population.
2. Absence of a statistically significantly higher risk of toxoplasmosis compared to healthy controls suggests that the relationship between it and DS is complex and could be influenced by numerous factors.
3. Factors that are involved in the relationship between toxoplasmosis and DS include immune deficiency, neurologic disorders and behavioral disabilities that causes sanitation challenges, environmental exposures, and comorbid health issues are other reasons.
4. Additional research should be conducted to clarify the intrinsic mechanisms responsible for the higher incidence of toxoplasmosis in these patients and to implement effective prevention strategies to reduce infection risk.
5. This study establishes an imperative foundation for large-scale prospective investigations to rigorously quantify *T. gondii* burden and clinical sequelae in individuals with DS, thereby guiding targeted prevention strategies.

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approval of the final version of the manuscript. Rahimi Esboei B, Sadeghi M and Gholami Sh revised the draft. Tork M and Sarvi Sh contributed in approving the search strategy. Hossieni SA analyzed data. Daryani A and Agayan SA contributed in the approval of the final version of the manuscript.

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