Jurnal Biosains Pascasarjana Vol. 26 (2024)

ANALYSIS OF SEIZURES IN PATIENTS WITH MOTHERS HAVING A HISTORY OF *Toxoplasma gondii* INFECTION

Francisca Cindy Meilia Apsari[1], Adelia Safira[2], Hanalda Wanda Hardiwan[3], Arif Rahman Nurdianto[4*]

[1,2,3] Department of Biomedical Engineering, Faculty of Intelligent Electrical and Informatics Technology, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia
[4]Toxoplasma Study Group, Institut of Tropical Disease, Universitas Airlangga, Indonesia
[*]E-mail : didins99@gmail.com

Abstrak

Toksoplasmosis adalah penyakit yang disebabkan oleh parasit Toxoplasma gondii, dengan prevalensi tinggi di Asia Tenggara, termasuk Indonesia. Infeksi ini dapat menyebabkan kerusakan otak dan berhubungan dengan penyakit seperti epilepsi. Penelitian ini bertujuan untuk menganalisis kejadian kejang pada pasien yang ibunya memiliki riwayat infeksi T. gondii. Toksoplasmosis selama kehamilan dapat ditularkan ke janin melalui plasenta, menyebabkan kerusakan jaringan janin yang parah dan berpotensi memicu gangguan neurologis seperti epilepsi. Mekanisme patofisiologis termasuk peningkatan permeabilitas sawar darah otak, eksitotoksisitas, kerusakan reseptor glutamatergik da mitokondria. Di Indonesia, prevalensi toksoplasmosis berkisar antara 40%-60%, dengan berbagai faktor risiko seperti kontak dengan kucing liar dan kebiasaan makan daging mentah. Studi ini menggunakan metode tinjauan literatur untuk menyelidiki hubungan antara infeksi T. gondii pada ibu dan kejadian epilepsi pada anak. Kesimpulan dari penelitian ini menunjukkan bahwa infeksi maternal T. gondii selama kehamilan secara signifikan meningkatkan risiko epilepsi pada keturunannya. Langkah-langkah kesehatan masyarakat yang efektif sangat diperlukan untuk meningkatkan kesadaran pencegahan dan akses ke perawatan prenatal yang komprehensif.

***Kata Kunci**: Epilepsi, Infeksi Maternal, Kehamilan, Toksoplasmosis*

Abstract

Toxoplasmosis is a disease caused by the parasite *Toxoplasma gondii*, with high prevalence in Southeast Asia, including Indonesia. This infection can cause brain damage and is associated with diseases such as epilepsy. This study aims to analyze the occurrence of seizures in patients whose mothers have a history of *T. gondii* infection. Toxoplasmosis during pregnancy can be transmitted to the fetus via the placenta, causing severe fetal tissue damage and potentially triggering neurological disorders like epilepsy. Pathophysiological mechanisms include increased blood-brain barrier permeability, excitotoxicity, and damage to glutamatergic receptors and mitochondria. In Indonesia, the prevalence of toxoplasmosis ranges from 40%-60%, with risk factors including contact with stray cats and consuming raw meat. This study utilizes a literature review method to investigate the relationship between maternal *T. gondii* infection and the incidence of epilepsy in offspring. The findings suggest that maternal *T. gondii* infection during pregnancy significantly increases the risk of epilepsy in offspring. Effective public health measures are crucial for raising prevention awareness and improving access to comprehensive prenatal care.

***Keywords**: Epilepsy, Maternal Infection, Pregnancy, Toxoplasmosis*

1. INTRODUCTION

Toxoplasmosis is a disease caused by the parasite *Toxoplasma gondii (T. gondii)*. Human infection with *T. gondii* is known to have a high prevalence, particularly in Southeast Asia, with reported rates ranging from 13.3% to 85.3% (Bisetegn et al., 2023). In Indonesia, the prevalence of infection is approximately 40%-60% (Dwi Pramardika

et al., 2022). This high prevalence is largely influenced by the tropical climate, which supports the survival of the parasite, and the high population of free-roaming cats. Other contributing factors include a lack of public awareness about prevention, suboptimal hygiene practices, and limited health education (Jayawardhana et al., 2023).

Several studies have indicated that *T. gondii* infection is associated with brain damage, leading to congenital diseases such as hydrocephalus and intracranial calcifications or neurological diseases such as epilepsy (Hutson et al., 2015a; Ngoungou et al., 2015; Vidal et al., 2022). Epilepsy affects men more often than women with the highest incidence in children in the first year of life, then declines to reach adult levels by the age of 10 years. Babies under a year old and adults over 50 are the most likely to have the disorder, which peaks in those over 70. About 5.6 out of 1,000 people in Indonesia have epilepsy and the annual incidence is almost 50 out of 100,000. Compared to certain other Asian nations, Indonesia has a comparatively high number of epileptic patients, indicating that epilepsy is a serious health issue there (Adamu et al., 2023).

Notably, *T. gondii* can invade and persist in neural tissues, leading to alterations in neurotransmitter systems, including gamma-aminobutyric acid (GABA) production, which plays a crucial role in inhibitory signaling in the brain (Brooks et al., 2015). Furthermore, *T. gondii* infection has been linked to disruptions in calcium (Ca^{2+}) channels, which are essential for normal neuronal function and signal transduction (Pace et al., 2014).

The parasite's presence in specific brain regions, such as the cortex and gray matter, has been associated with structural and functional abnormalities. These regions are critical for higher cognitive functions, sensory processing, and motor control (Hutson et al., 2015a). The infection also triggers an immune response, leading to the release of pro-inflammatory cytokines and other immune mediators (Hutson et al., 2015a). These inflammatory processes can further exacerbate neural damage and contribute to the pathophysiology of epilepsy.

This study aims to analyze the occurrence of seizures in patients whose mothers have a history of *T. gondii* infection. Understanding the link between maternal toxoplasmosis and the development of epilepsy in offspring is crucial for improving prevention strategies and management of epilepsy in Indonesia. By examining this relationship, we hope to provide insights that can lead to better health outcomes for affected populations.

2. TOXOPLASMOSIS INFECTION IN PREGNANCY

Toxoplasmosis infection during pregnancy can pose significant risks, including the potential for miscarriage and congenital diseases. The parasite can increase levels of ICAM1 and serotonin (5-HT), which trigger the migration of mast cells to the infection site. This immune response can lead to decreased submucosal thickness and disruption of extracellular matrix (ECM) formation, further complicating the pregnancy (Nurdianto & Suryokusumo, 2019).

Toxoplasmosis infection during pregnancy can lead to an imbalance between Th1 and Th2 immune responses, which are crucial for maintaining immune homeostasis. Th1 cells are typically associated with pro-inflammatory responses, while Th2 cells are involved in anti-inflammatory and humoral immunity. Additionally, *T. gondii* infection can disrupt the regulation of interleukin-17 (IL-17), a cytokine produced by Th17 cells that plays a role in inflammation and autoimmunity. This disturbance in IL-17 regulation can exacerbate the immune response against the parasite, leading to increased tissue damage and a higher risk of adverse outcomes such as preterm birth, fetal growth restriction, or congenital malformations (Nurdianto et al., 2020).

2.1 Transmission and Impact on the Fetus

tachyzoite, and bradyzoite (García et al., 2021). The life cycle begins when a pregnant

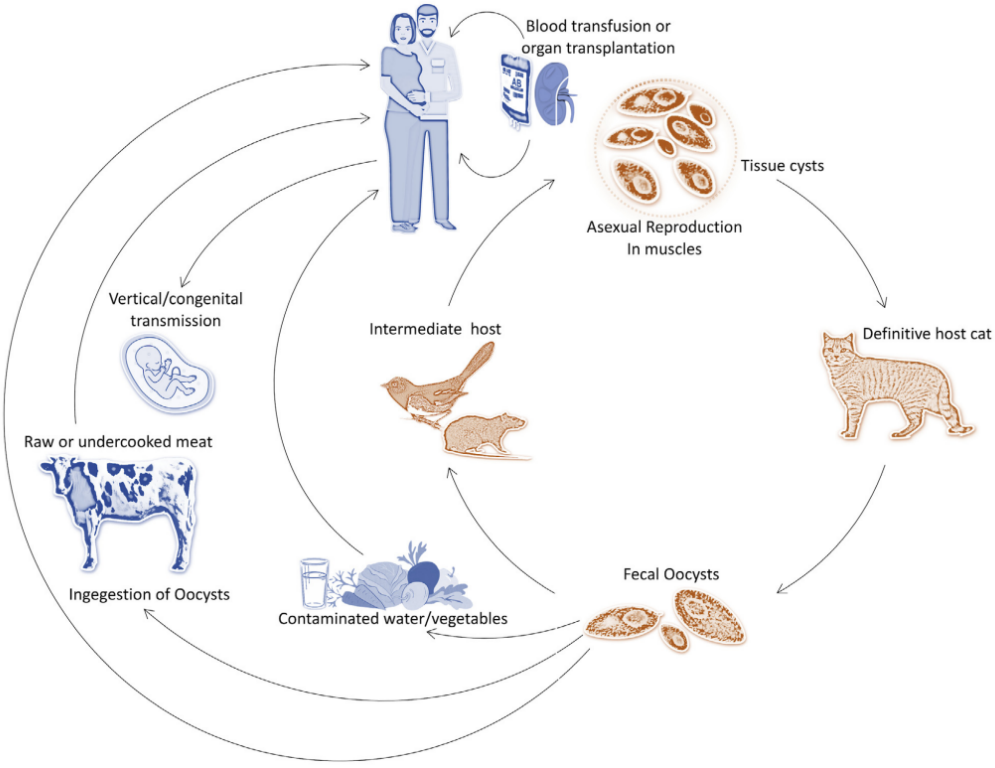

Figure 1. Transmission of *T. gondii* (S. Al-Malki, 2021)

During pregnancy, toxoplasmosis can be transmitted to the fetus via the placenta, leading to severe fetal tissue damage. If the parasite crosses the placental barrier, it can invade the fetal bloodstream and replicate within neural cells, causing direct cellular destruction. This invasion triggers a robust inflammatory response as the immune system attempts to combat the infection. The resulting inflammation can further exacerbate brain damage by disrupting normal brain development and function. The combination of direct parasitic destruction of neural cells and the inflammatory response increases the risk of long-term complications, such as congenital diseases and neurological disorders including chorioretinitis, intracranial calcifications, and seizures (Chaudhry et al., 2014; Deganich et al., 2023).

2.2 Stages of *T. gondii* in Pregnancy

T. gondii has a complex life cycle that involves several stages: sporozoite,

woman ingests oocysts, the environmentally resistant form of *T. gondii*. As can be seen from Figure 1 (S. Al-Malki, 2021), oocysts are typically acquired through consumption of contaminated food or water, contact with soil, or handling cat litter. These oocysts are produced in the intestines of infected cats and excreted in their feces. Once in the environment, the oocysts undergo sporulation, becoming infectious. When a pregnant woman ingests these oocysts, they release sporozoites in her digestive tract.

Upon ingestion, the sporozoites are released from the oocysts and invade the epithelial cells of the intestine. Inside these cells, the sporozoites transform into tachyzoites, the rapidly multiplying and invasive form of the parasite. Tachyzoites disseminate through the bloodstream and lymphatic system, spreading the infection to various tissues throughout the body, including the placenta. This stage represents the acute phase of toxoplasmosis, which can cause mild flu-like symptoms in the mother or remain asymptomatic (Peyron et al.,

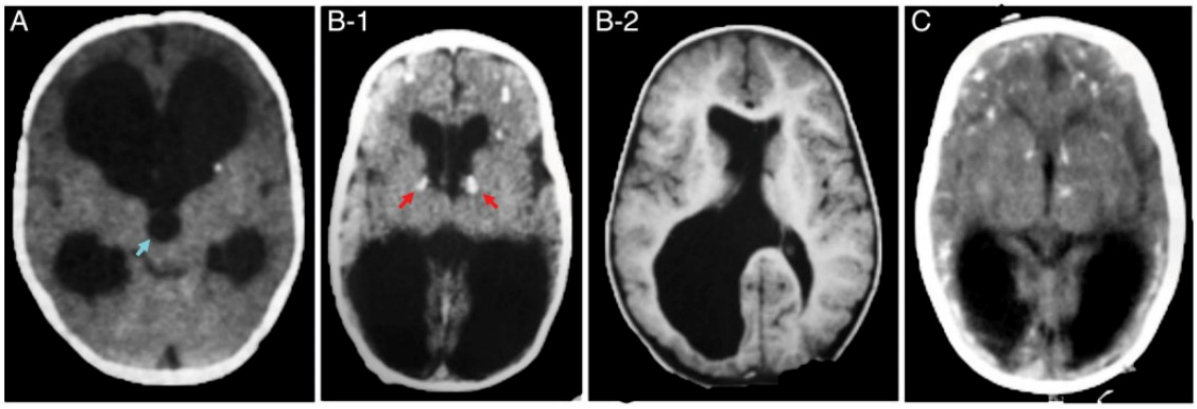

Figure 2. Examples of CT scans of types of hydrocephalus and brain damage caused by congenital toxoplasmosis that can affect the brain (Hutson et al., 2015b)

2019). Tachyzoites can cross the placental barrier, especially if the mother acquires the infection for the first time during pregnancy. The risk of transmission to the fetus varies with the gestational age: it is lower in the first trimester but can cause more severe fetal damage, while it is higher in the later trimesters with generally milder outcomes (Chaudhry et al., 2014). Once the tachyzoites reach the placenta, they can invade fetal tissues, leading to congenital infection. The placenta itself can become inflamed and damaged, which can impair its function and contribute to adverse pregnancy outcomes.

In the fetus, tachyzoites continue to replicate and invade various organs, particularly the brain, eyes, and muscles. This invasion can cause significant damage, including inflammation, necrosis, and the formation of tissue cysts. These cysts contain bradyzoites, a slower-replicating form of the parasite that can persist in the tissues for the lifetime of the host.

3. THE OCCURRENCE OF EPILEPSY IN CHILDREN WITH MOTHERS WHO HAVE A HISTORY OF TOXOPLASMOSIS INFECTION

The global prevalence of latent toxoplasmosis in pregnant women was found to be 33.8%. Pregnant women who contract *Toxoplasma gondii* infection have the risk of their fetus having problems at birth such as brain damage which can eventually lead to epilepsy. Infections such as hydrocephalus, intracranial calcifications, and retinal disorders can all be caused by congenital toxoplasmosis which occurs when the virus is transmitted from mother to fetus and increases the risk of the child developing epilepsy (Rostami et al., 2020). That hydrocephalus brought on by an infection with congenital toxoplasmosis can seriously harm brain tissue, which can lead to the onset of epileptic episodes. One of the signs of congenital toxoplasmosis that can cause significant brain damage is hydrocephalus. This condition can also cause vasculitis and necrosis that impact the periaqueductal and periventricular regions of the brain, which can ultimately lead to epileptic episodes.

Congenital toxoplasmosis causes hydrocephalus and brain damage, as seen in Figure 2. Blue arrows in Figure A represent increased cerebrospinal fluid (CSF) accumulation and hydrocephalus with enlarged ventricles. Periventricular calcifications, characteristic of congenital toxoplasmosis, are indicated by red arrows in Figure B-1. Ventricular dilatation is severe, as seen in Figure B-2. Advanced ventricular hypertrophy and structural anomalies are depicted in Figure C. Intraventricular blockages are categorized in Figure D using color-coded segments that correspond to different situations. (Hutson et al., 2015b)

The two types of hydrocephalus are classed as communicative and non-communicating. Communicative hydrocephalus is caused by an accumulation of fluid in the brain ventricles without any blockage between them. The term "obstructive cerebrospinal fluid (CSF)" refers to CSF that is unable to flow correctly

between the ventricles due to a blockage in the ventricular system. Congenital abnormality or infection is often the source of this fluid buildup. (Hutson et al., 2015) The digestive system is the route of the spread of toxoplasmosis, usually through contaminated food or drink. Pregnant women infected with the virus are often asymptomatic which can lead to miscarriage or fetal abnormalities, including central and peripheral nervous system problems. One of the causes of this virus is epileptic seizures (Wahyuni, 2013).

3.1 Pathophysiologic Mechanisms of Epilepsy in Children of Mothers with Toxoplasmosis Infection

A mother's toxoplasma infection can result in multiple interconnected pathogenic pathways that lead to epilepsy in her child. First, the infection makes the Blood-Brain Barrier (BBB) more permeable, which makes it possible for dangerous chemicals to reach the brain. Glutamatergic receptor activation as a result of increased BBB permeability subsequently causes excitotoxicity and mitochondrial damage. Impaired neural function is partly caused by mitochondrial injury. The ensuing effects of increased BBB permeability-induced glutamatergic receptor activation are excitotoxicity and mitochondrial damage. When NMDA receptors are over-stimulated, toxic calcium ions enter the neurons, impairing mitochondrial activity and oxidative stress. The increase in intracellular calcium stimulates the opening of the mitochondrial permeability transition pore (mPTP), which exacerbates cell damage and aggravates neurodegeneration, ultimately leading to impaired neuronal function. (Verma et al., 2022)

Moreover, autophagy and the Ubiquitin-Proteasome System (UPS) can be interfered with by *T. gondii* infection, leading to an imbalance in excitatory and inhibitory neurotransmission and an increase in neuronal excitability. When pro-apoptotic pathways are activated by an overabundance of glutamate receptors, neuronal cell death occurs either by autophagy or apoptosis. Inflammatory processes exacerbate the disease and promote the onset of epilepsy by increasing neuronal excitability and BBB permeability through the release of cytokines like IL-1β. When combined, these pathways raise the chance of epilepsy in kids whose moms had a history of Toxoplasma infection (Sumadewi et al., 2023).

3.2 BBB Structure Changes in Epilepsy

The blood-brain barrier's (BBB) structural alterations impact the BBB's functionality in epileptic situations. Angiogenesis, the creation of new blood vessels brought on by pathological and rheological signals, is one of the primary alterations. This process results in aberrant vascular remodeling and the development of new microvessels, particularly in epileptic areas in individuals with drug-resistant Temporal Lobe Epilepsy (TLE) and in TLE experimental models. The breakdown of tight connections between blood vessel cells frequently coexists with this aberrant angiogenesis, making the blood-brain barrier more permeable to molecules like immunoglobulin G (Ig G) that shouldn't be able to pass through it (Löscher & Friedman, 2020).

Studies with the use of electron microscopy revealed that in the epileptic brain, there was increased pinocytosis activity, abnormalities in tight junctions, and thickening of the basement membrane. Due to increased pinocytosis activity, it is possible that endothelial cells in the blood arteries of the brain actively absorb blood and fluid components that disrupt the blood-brain barrier, supporting damage to the BBB. In epilepsy, there are morphological and functional changes in astrocytes, which are supporting cells in the brain. This includes modifications to its ability to regulate neurotransmitter levels, interactions with neurons, and inflammatory responses. These changes can also affect gliotransmitter release, disrupt potassium (K+) buffering, limit glutamate uptake, and lead to neuronal hyperexcitability and seizures. Reactive astrogliosis, characterized by hypertrophy and proliferation of astrocytes in response to

epileptic activity, exacerbates neuronal dysfunction and tissue instability. (Bollani et al., 2022)

The capacity of BBB's ability to maintain neurons in a stable environment may be affected by these astrocyte changes which also include modifications in the expression of (K+) and water channels (Löscher & Friedman, 2020). A clinical review of the Kv family, in which abnormalities in (K+) channel expression and function can lead to seizures by upsetting neuronal excitability and electrolyte balance. K+ channels have a role in controlling nerve cell repolarization and membrane potential. Mutations in genes like KCNQ2 and KCNQ3 can cause K+ channels to become dysfunctional or to function differently, which can cause excessive depolarization and uncontrollable electrical activity, which can cause seizures. Examples in particular are mutations linked to epilepsy that manifest in newborns. (Allen et al., 2020)

4. EPIDEMIOLOGY OF EPILEPSY IN CHILDREN WITH MOTHERS WHO HAVE A HISTORY OF TOXOPLASMOSIS INFECTION

In Indonesia, where 49.8% of the population is female and 28.32% of them report health issues, pregnancy and childbirth are the riskiest times for women. 25,629 baby deaths and 4,614 maternal deaths were reported in Indonesia in 2020. Because women are primarily responsible for bearing children, maternal and newborn mortality is a major issue. With a 25.2% prevalence, Indonesia has a high intrauterine fetal death (IUD) rate. To identify the underlying cause of fetal mortality, an autopsy is necessary. Possible causes include maternal, baby, placental, or medical intervention factors. Three to four percent of fetal deaths are attributed to toxoplasma infection, which is brought on by *T. gondii* and is a common cause of abortion or stillbirth. The risk of infection is higher in pregnant women (Dwi Pramardika et al., 2022).

Toxoplasmosis was most prevalent in Jambi city (60%), Bantul (55.6%), Minahasa (50%), Samarinda (43.5%), and Makassar (40%), corresponding to the spread of the disease among Indonesian women. Prevalence of stray cats, occupation, eating raw or undercooked meat, parity status, not wearing shoes outside the home, and owning poultry were the greatest risk factors for toxoplasmosis among Indonesian women. With a prevalence of 40-60%, toxoplasma infection has become widespread throughout Indonesia, exceeding neighboring countries such as Malaysia (42.5%). Toxoplasma parasites, which are more commonly found in subtropical and tropical countries, thrive in tropical Indonesia. The parasite reproduces sexually in feline hosts, where its oocysts can live in warm, moist soil for up to a year. Infected adult oocysts can infect intermediate hosts, including people, pigs, birds, mice, and goats (Dwi Pramardika et al., 2022).

5. POTENTIAL BRAIN DAMAGE IN INFANTS INFECTED WITH TOXOPLASMOSIS RESULTING IN EPILEPSY

When an infant has seizures or epilepsy due to congenital toxoplasmosis, the seizures are often focal in nature. Focal seizures, also known as partial seizures, originate in a specific area of the brain and can manifest as either simple or complex. In simple focal seizures, consciousness remains intact, while complex focal seizures involve impaired awareness. These seizures may present with symptoms such as jerking movements in one part of the body, altered sensory perceptions, or behavioral changes. The focal nature of these seizures is attributable to the localized brain damage caused by the *T. gondii* infection, which often leads to the formation of cysts in specific brain regions.

In terms of EEG (electroencephalogram) findings, the most commonly affected brain waves during

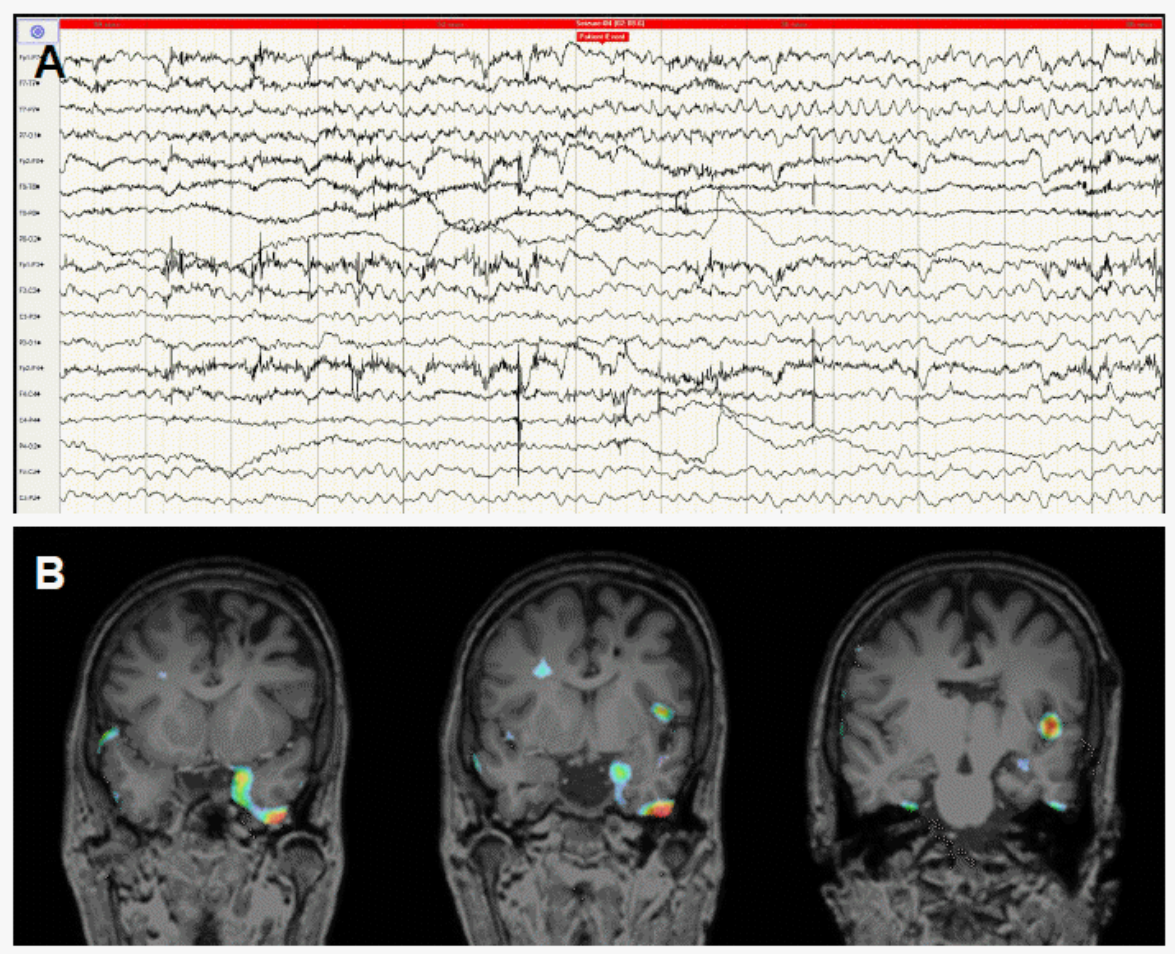

Figure 3. (A)The ictal EEG recording shows that the seizure starts with delta waves in the left temporal area and develops into rhythmic theta waves spreading to the left hemisphere. (B) The SISCOM images show a hyperperfusion zone in the left temporal area during the seizure

seizures due to toxoplasmosis are typically the delta waves. Delta waves are slow brain waves with a frequency of 0.5 to 4 Hz, usually associated with deep sleep in healthy individuals. However, in the context of seizure activity, these waves can appear as abnormal slow wave patterns, indicating areas of brain dysfunction (Chou et al., 2020). Additionally, interictal (between seizures) EEG may show focal spikes or sharp waves, particularly in the regions where the brain has been structurally compromised by the infection.

In Figure 3. the seizure starts with delta waves in the left temporal area, which then develop into rhythmic theta waves that spread throughout the left hemisphere. on SPECT images usually show areas of different activity: Hyperperfusion (lighter color) e.g., green, yellow, and red indicates areas that are more metabolically active during seizures. Areas with high activity are associated with seizures. Hypoperfusion (darker color) indicates areas that are less active or have decreased blood flow. (Jeong et al., 2015)

The part of the brain most responsible for seizures in congenital toxoplasmosis is often the cortex, Specifically, the areas affected by the formation of toxoplasmic cysts are a significant aspect of *T. gondii* infections, particularly in the brain and on nerve tissue, where it forms cysts, triggers inflammation, and alters nerve function, leading to potential cognitive and behavioral changes, causing inflammation and scarring (gliosis) in the brain tissue, and leading to

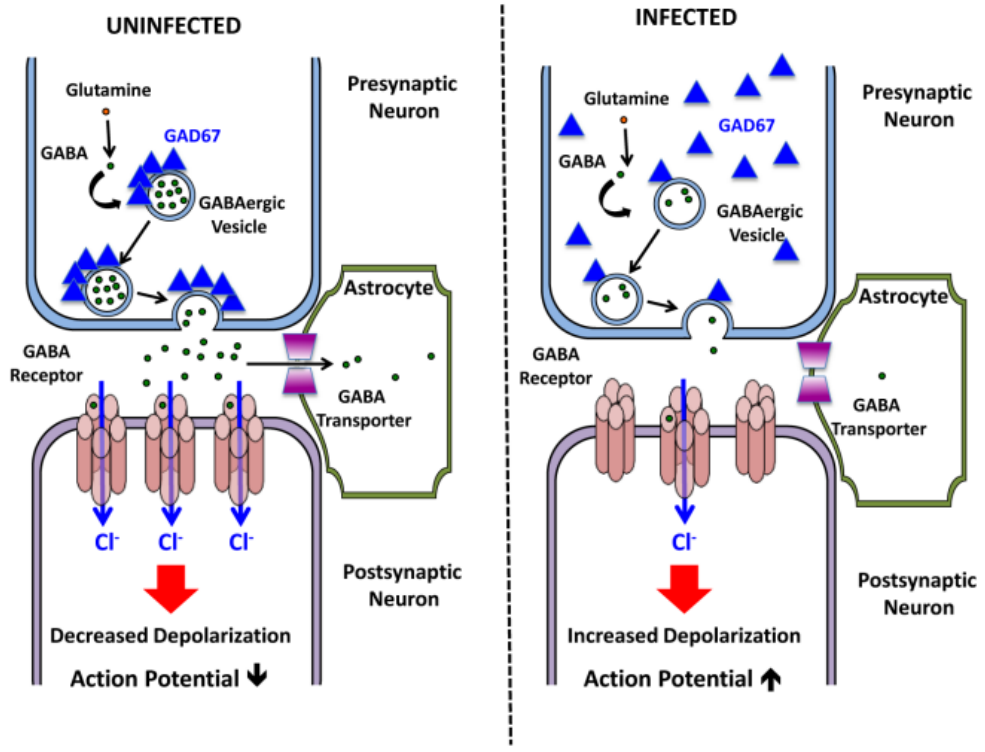

Figure 4. Toxoplasma Modifies the Localization of GAD67 to Reduce Inhibitory GABAergic Synaptic Transmission

increased excitability of the neurons in the affected regions (Erickson et al., 2021). The cerebral cortex, particularly the temporal lobes, is frequently involved in focal seizures. The temporal lobes are critical for processing sensory input and encoding memory, and their involvement can result in complex symptoms such as sensory disturbances and automatisms (repetitive, involuntary actions). The propensity for seizures is heightened in these areas due to the disruption of normal neural circuits and the creation of a hyperexcitable state in the cortex.

Neural circuits, which are networks of interconnected neurons, rely on a delicate balance of excitatory and inhibitory signals to function correctly. Normal synaptic activity requires a balance of excitatory and inhibitory neurotransmissions. GABA is the brain's principal inhibitory neurotransmitter, produced primarily by glutamate decarboxylase 67 (GAD67). As can be seen in Figure 4 (Wohlfert et al., 2017), in Toxoplasma-infected brains, GAD67 localization shifts from synaptic vesicles to diffuse throughout the cell. GAD67 localization changes may limit its ability to manufacture GABA, resulting in reduced GABAergic signaling. Research in Toxoplasma-infected mice shows that they exhibit longer and more severe convulsions when treated with GABA receptor antagonists. Seizures in these mice result from alterations in both excitatory and inhibitory neurotransmission. While this research is based on mice, it may also have implications for understanding how Toxoplasma infection could affect human brain function and potentially lead to seizures.

6. RESEARCH METHOD

This study utilizes a literature review method to investigate the relationship between maternal *Toxoplasma gondii* infection and the incidence of epilepsy in offspring. The literature review involved a comprehensive search and analysis of peer-reviewed articles, systematic reviews, and meta-analyses. Key databases, including PubMed, Google Scholar, and specialized journals, were used to gather relevant studies published from 2013 up to 2024. The

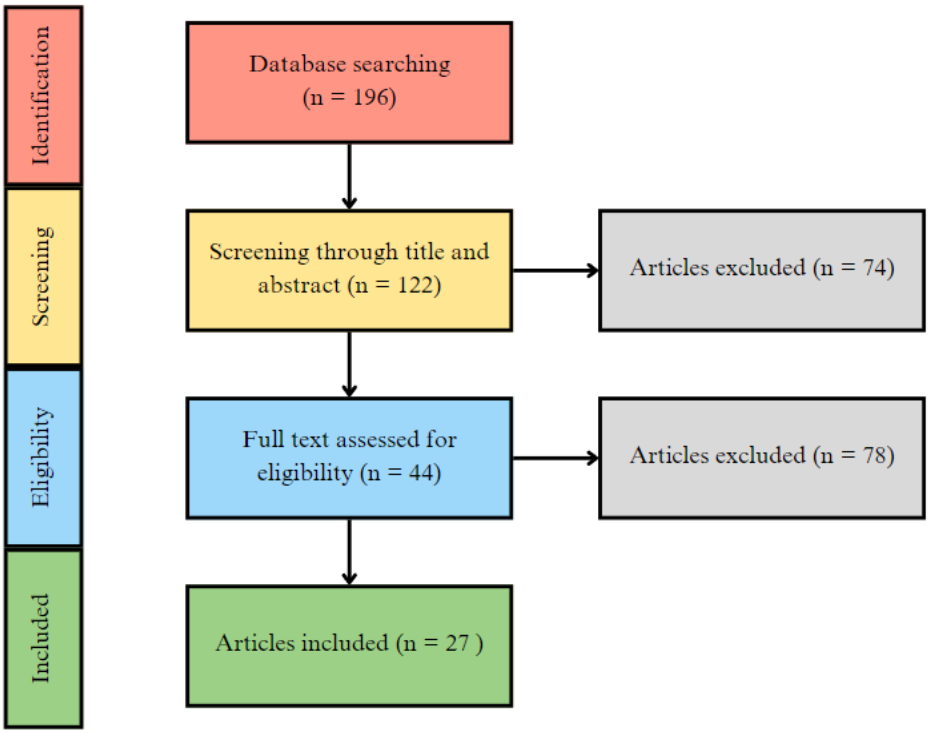

Figure 5. Literature Review Method Diagram

selection criteria focused on studies that explored the prevalence of *T. gondii* infection during pregnancy, its impact on fetal development, and its association with neurological disorders, particularly epilepsy. As can be seen in Figure 5, the initial search yielded a total of 196 articles, which were subsequently screened by examining their titles and abstracts. The final selection comprised 27 articles that is used for this study.

7. RESULTS AND DISCUSSION

7.1 Effects of Toxoplasmosis Infection on Pregnancy Outcomes

Toxoplasmosis can disrupt normal immune regulation, particularly by affecting the balance between Th1 and Th2 immune responses, which are crucial for maintaining immune homeostasis. The infection's ability to upregulate ICAM1 and serotonin (5-HT) suggests an inflammatory response that can attract mast cells to the infection site, potentially causing tissue damage. The subsequent decrease in submucosal thickness and disruption of extracellular matrix (ECM) formation may compromise placental integrity and function, contributing to adverse pregnancy outcomes such as miscarriage, preterm birth, or fetal growth restriction.

Additionally, the disruption of interleukin-17 (IL-17) regulation and its role in inflammation and autoimmunity further complicates the immune response. IL-17's involvement in enhancing inflammation could exacerbate tissue damage and increase the risk of adverse fetal outcomes, such as congenital malformations. The combined effects of immune dysregulation and direct parasitic invasion highlight the complex pathophysiology of toxoplasmosis during pregnancy, underlining the need for vigilant monitoring and potential therapeutic interventions to mitigate risks to both the mother and fetus.

7.2 Fetal Transmission and Neurological Impact

The parasite's ability to cross the placental barrier and invade the fetal bloodstream enables it to infect neural cells directly, leading to cellular destruction. This invasion is compounded by the host's immune response, which, while attempting to combat the infection, can inadvertently exacerbate brain damage through

inflammation. The inflammatory response can disrupt normal brain development and function, increasing the risk of long-term complications such as chorioretinitis, intracranial calcifications, and seizures.

These neurological effects are particularly concerning given their potential to result in lifelong disabilities. The parasite's preference for neural tissues, including the brain and eyes, means that even subclinical infections can lead to significant developmental issues. The extent of damage depends on the gestational age at which the infection occurs, with earlier infections typically resulting in more severe outcomes.

7.3 Relationship Between Maternal Toxoplasmosis and Offspring Epilepsy

The epidemiological data indicates a significant correlation between maternal toxoplasmosis infection and the incidence of epilepsy in offspring. The global prevalence of latent toxoplasmosis among pregnant women is concerning, given the potential for severe fetal neurological outcomes. Conditions such as hydrocephalus, intracranial calcifications, and retinal disorders, often associated with congenital toxoplasmosis, have been identified as potential precursors to epilepsy. The structural brain abnormalities caused by these conditions can disrupt normal neural circuitry, leading to seizures.

Hydrocephalus is a major concern due to its potential to cause severe brain tissue damage, vasculitis, and necrosis, particularly in the periaqueductal and periventricular regions. These regions are crucial for maintaining normal brain function, and damage here can predispose infants to seizures. The differentiation between communicating and non-communicating hydrocephalus also highlights the diverse pathways through which congenital toxoplasmosis can lead to epilepsy. This emphasizes the need for comprehensive prenatal screening and postnatal monitoring in children born to mothers with toxoplasmosis to manage and mitigate the risk of epilepsy.

7.4 Pathophysiological Mechanisms of Epilepsy Due to Toxoplasmosis

The pathophysiological mechanisms linking maternal toxoplasmosis infection to epilepsy in offspring involve multiple interconnected pathways. The breach of the Blood-Brain Barrier (BBB) by the infection allows harmful substances to penetrate the brain, triggering excitotoxicity and mitochondrial damage. This process is exacerbated by the activation of glutamatergic receptors, leading to excessive calcium influx into neurons, mitochondrial dysfunction, and oxidative stress. The resulting neuronal damage contributes to a state of heightened excitability and predisposes the brain to epileptic seizures.

Furthermore, the interference with autophagy and the Ubiquitin-Proteasome System (UPS) by *T. gondii* infection leads to an imbalance between excitatory and inhibitory neurotransmission. The disruption in glutamate receptor regulation and subsequent neuronal cell death due to apoptosis or autophagy creates a neurotoxic environment. Inflammatory responses, particularly involving cytokines like IL-1β, further exacerbate neuronal excitability and BBB permeability, creating a vicious cycle that increases the risk of epilepsy. These findings underscore the importance of targeting these specific pathways for therapeutic intervention to prevent or reduce the severity of epilepsy in affected children.

7.5 Structural Changes in the Blood-Brain Barrier and Epilepsy

The structural changes in the BBB in epileptic conditions, particularly in the context of congenital toxoplasmosis, are profound. Abnormal angiogenesis, increased pinocytosis activity, and tight junction disruptions are key features that compromise BBB integrity. The formation of new microvessels in response to pathological signals can lead to an increased permeability of the BBB, allowing substances such as immunoglobulin G (IgG) to infiltrate the brain. These changes are particularly evident in areas prone to seizures, such as the

temporal lobes, where abnormal angiogenesis and BBB breakdown are more pronounced.

Additionally, astrocyte dysfunction plays a significant role in the pathophysiology of epilepsy. Reactive astrogliosis, characterized by the proliferation and hypertrophy of astrocytes in response to brain injury or inflammation, can lead to disrupted potassium and water homeostasis. These changes impair the astrocytes' ability to buffer potassium and glutamate levels, exacerbating neuronal hyperexcitability and seizure susceptibility. The modification of ion channel expression, particularly potassium channels, further contributes to the destabilization of neuronal networks

7.6 Epidemiology and Risk Factors of Toxoplasmosis-Related Epilepsy

The epidemiology of toxoplasmosis-related epilepsy reveals a high prevalence of toxoplasma infection in certain regions, notably in Indonesia. The high prevalence rates in areas such as Jambi City, Bantul, and Minahasa indicate a significant public health challenge. Factors such as exposure to stray cats, consumption of undercooked meat, and environmental conditions conducive to the survival of *T. gondii* oocysts contribute to the widespread nature of the infection. The correlation between these factors and the high rate of congenital toxoplasmosis underscores the need for public health interventions, such as educating the population about safe food handling practices and controlling stray cat populations.

The data also highlight the importance of maternal screening for toxoplasmosis, particularly in regions with high infection rates. Pregnant women are often asymptomatic, yet the risk of severe outcomes, including stillbirth, intrauterine fetal death, and congenital anomalies, is significant. The association between maternal toxoplasmosis and central nervous system abnormalities in offspring, including epilepsy, further emphasizes the need for vigilant prenatal care and appropriate treatment to prevent or mitigate the impact of this infection.

7.7 Potential for Brain Damage and Seizures in Infants

The potential for brain damage in infants born to mothers with toxoplasmosis is a critical area of concern. The formation of toxoplasmic cysts in the brain can lead to localized damage, resulting in focal seizures. These seizures, which can be simple or complex depending on the level of consciousness, often manifest with symptoms such as jerking movements, altered sensory perceptions, or behavioral changes. The localized nature of these seizures is indicative of the specific brain regions affected by the infection, with the temporal lobes being particularly vulnerable.

EEG findings in infants with congenital toxoplasmosis often show abnormal delta waves, indicative of slow wave activity associated with brain dysfunction. The presence of focal spikes or sharp waves interictally also points to localized areas of neuronal instability. Functionalings suggest that the structural and functional changes induced by toxoplasmosis can create a hyperexcitable state in the brain, predisposing these infants to recurrent seizures and potentially leading to the development of epilepsy.

8. CONCLUSIONS AND SUGGESTIONS

Analysis of the pathophysiology of epilepsy in offspring of mothers infected with *T. gondii* revealed important processes involving GABA and the blood-brain barrier (BBB). Excitotoxic chemicals can enter the brain due to the BBB's increased permeability caused by *T. gondii* infection, which breaks down the barrier's integrity. Excitotoxicity, which is defined by an excessive amount of NMDA receptor stimulation and a hazardous calcium ion inflow into neurons, is the result of the activation of glutamatergic receptors. Epilepsy develops as a result of the oxidative stress and mitochondrial malfunction that follow, which compromise neural activity.

In addition, these infections disrupt GABAergic signaling, which is the brain's inhibitory mechanism. Increased neuronal excitability and a higher risk of seizures result

from the redistribution of glutamate decarboxylase 67 (GAD67), an enzyme required for GABA synthesis, which decreases GABA levels. In addition, inflammatory cytokines such as IL-1β are induced by infection and exacerbate BBB permeability and neuronal excitability. If a woman has a history of Toxoplasma infection during pregnancy, these interrelated pathways result in a neurotoxic environment that predisposes the infant to epilepsy. By knowing these pathways, we can identify possible treatment targets to reduce the likelihood of affected individuals having seizures.

More research is required to develop more sustainable technology perhaps in the future, a radar-like gadget that looks at the fetus's electrical activity will be able to identify epileptic episodes in the fetal brain.

ACKNOWLEDGEMENT

Regarding Dr. Abdillah Segaf Al Hadad, MM, the director of Sidoarjo Barat Regional General Hospital, we would like to express our sincere gratitude. We were able to finish the paper titled "Analysis of Seizures in Patients with Mothers Having a History of *Toxoplasma gondii* Infection" with his help and direction. The wonderful assistance we received from Dr. Abdillah Segaf Al Hadad, MM, has greatly inspired and motivated us to finish this study.

BIBLIOGRAPHY

Adamu, A., Chen, R., Li, A., & Xue, G. (2023). Epilepsy in Asian countries. In *Acta Epileptologica* (Vol. 5, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s42494-023-00136-1

Allen, N. M., Weckhuysen, S., Gorman, K., King, M. D., & Lerche, H. (2020). Genetic potassium channel-associated epilepsies: Clinical review of the Kv family. In *European Journal of Paediatric Neurology* (Vol. 24, pp. 105–116). W.B. Saunders Ltd. https://doi.org/10.1016/j.ejpn.2019.12.002

Bisetegn, H., Debash, H., Ebrahim, H., Mahmood, N., Gedefie, A., Tilahun, M., Alemayehu, E., Mohammed, O., & Feleke, D. G. (2023). Global seroprevalence of *Toxoplasma gondii* infection among patients with mental and neurological disorders: A systematic review and meta-analysis. *Health Science Reports*, *6*(6). https://doi.org/10.1002/hsr2.1319

Bollani, L., Auriti, C., Achille, C., Garofoli, F., De Rose, D. U., Meroni, V., Salvatori, G., & Tzialla, C. (2022). Congenital Toxoplasmosis: The State of the Art. In *Frontiers in Pediatrics* (Vol. 10). Frontiers Media S.A. https://doi.org/10.3389/fped.2022.894573

Brooks, J. M., Carrillo, G. L., Su, J., Lindsay, D. S., Fox, M. A., & Blader, I. J. (2015). *Toxoplasma gondii* infections alter GABAergic synapses and signaling in the central nervous system. *MBio*, *6*(6). https://doi.org/10.1128/mBio.01428-15

Chaudhry, S. A., Gad, N., & Koren, G. (2014). Toxoplasmosis and pregnancy. *Canadian Family Physician Medecin de Famille Canadien*, *60*(4), 334–336.

Chou, P., Wang, G. H., Hsueh, S. W., Yang, Y. C., & Kuo, C. C. (2020). Delta-Frequency Augmentation and Synchronization in Seizure Discharges and Telencephalic Transmission. *IScience*, *23*(11). https://doi.org/10.1016/j.isci.2020.101666

Deganich, M., Boudreaux, C., & Benmerzouga, I. (2023). Toxoplasmosis Infection during Pregnancy. In *Tropical Medicine and Infectious Disease* (Vol. 8, Issue 1). MDPI. https://doi.org/10.3390/tropicalmed8010003

Dwi Pramardika, D., Disye Kasaluhe, M., Sambeka, Y., Negeri, P., Utara, N., Sangihe, K., & Utara, S. (2022). *Studi Literatur: Analisis Faktor Risiko Toksoplasmosis pada Wanita Indonesia*.

García, G. Á., Davidson, R., Jokelainen, P., Klevar, S., Spano, F., & Seeber, F. (2021). Identification of oocyst-driven *Toxoplasma gondii* infections in humans and animals through stage-specific serology— current status and future perspectives. In *Microorganisms* (Vol. 9, Issue 11). MDPI. https://doi.org/10.3390/microorganisms9112346

Hutson, S. L., Wheeler, K. M., McLone, D., Frim, D., Penn, R., Swisher, C. N., Heydemann, P. T., Boyer, K. M., Noble, A. G., Rabiah, P., Withers, S., Montoya, J. G., Wroblewski, K., Karrison, T., Grigg, M. E., & McLeod, R. (2015a). Patterns of Hydrocephalus Caused by Congenital *Toxoplasma gondii* Infection Associate with Parasite Genetics. *Clinical Infectious Diseases*, *61*(12), 1831–1834. https://doi.org/10.1093/cid/civ720

Hutson, S. L., Wheeler, K. M., McLone, D., Frim, D., Penn, R., Swisher, C. N., Heydemann, P. T., Boyer, K. M., Noble, A. G., Rabiah, P., Withers, S., Montoya, J. G., Wroblewski, K., Karrison, T., Grigg, M. E., & McLeod, R. (2015b). Patterns of Hydrocephalus Caused by Congenital *Toxoplasma gondii* Infection Associate with Parasite Genetics. *Clinical Infectious Diseases*, *61*(12), 1831–1834. https://doi.org/10.1093/cid/civ720

Jayawardhana, A., Harnida, H., Purwatiningsih, D., Puspitasari, H., Mufasirin, Suwanti, L. T., & Nurdianto, A. R. (2023). Seroprevalensi Kasus Toxoplasmosis sebagai Infeksi Oportunistik pada Penderita HIV/ Acquired Immune Deficiency Syndrome (AIDS) Di Kabupaten Sidoarjo. *NERSMID : Jurnal Keperawatan Dan Kebidanan*, *6*(1), 1–6. https://doi.org/10.55173/nersmid.v6i1.133

Jeong, W. K., Joo, B.-E., Seo, J.-H., Mun, J. K., Kim, J., & Seo, D.-W. (2015). *Mesial Temporal Lobe Epilepsy in Congenital Toxoplasmosis: A Case Report*. www.kes.or.kr

Löscher, W., & Friedman, A. (2020). Structural, molecular, and functional alterations of the blood-brain barrier during epileptogenesis and epilepsy: A cause, consequence, or both? In *International Journal of Molecular Sciences* (Vol. 21, Issue 2). MDPI AG. https://doi.org/10.3390/ijms21020591

Ngoungou, E. B., Bhalla, D., Nzoghe, A., Dardé, M. L., & Preux, P. M. (2015). Toxoplasmosis and Epilepsy — Systematic Review and Meta Analysis. *PLoS Neglected Tropical Diseases*, *9*(2). https://doi.org/10.1371/journal.pntd.0003525

Nurdianto, A. R., & Suryokusumo, M. G. (2019). Downregulates of ICAM1 expression in Myometrium from pregnant Rattus norvegicus infected with Tachyzoite of *Toxoplasma gondii* with Hyperbaric Oxygen Therapy. In *Nurdianto et. all, HTMJ* (Vol. 17, Issue 1). www.journal-medical.hangtuah.ac.id

Nurdianto, A. R., Suwanti, L., & Aryati, A. (2020). Effect of hyperbaric oxygen therapy on ICAM-1 expression in artery spiralis of pregnant Rattus norvegicus infected by Tachyzoite from *Toxoplasma gondii.* In *Article in Eurasian Journal of Biosciences*. https://www.researchgate.net/publication/354006503

Pace, D. A., McKnight, C. A., Liu, J., Jimenez, V., & Moreno, S. N. J. (2014). Calcium entry in *Toxoplasma gondii* and its enhancing effect of invasion-linked traits. *Journal of Biological Chemistry*, *289*(28), 19637–19647. https://doi.org/10.1074/jbc.M114.565390

Peyron, F., L'ollivier, C., Mandelbrot, L., Wallon, M., Piarroux, R., Kieffer, F., Hadjadj, E., Paris, L., & Garcia-Meric, P. (2019). Maternal and congenital toxoplasmosis: Diagnosis and treatment recommendations of a French multidisciplinary working group.

Pathogens, *8*(1). https://doi.org/10.3390/pathogens8010024

Rostami, A., Riahi, S. M., Gamble, H. R., Fakhri, Y., Nourollahpour Shiadeh, M., Danesh, M., Behniafar, H., Paktinat, S., Foroutan, M., Mokdad, A. H., Hotez, P. J., & Gasser, R. B. (2020). Global prevalence of latent toxoplasmosis in pregnant women: a systematic review and meta-analysis. In *Clinical Microbiology and Infection* (Vol. 26, Issue 6, pp. 673–683). Elsevier B.V. https://doi.org/10.1016/j.cmi.2020.01.008

S. Al-Malki, E. (2021). Toxoplasmosis: stages of the protozoan life cycle and risk assessment in humans and animals for an enhanced awareness and an improved socio-economic status. In *Saudi Journal of Biological Sciences* (Vol. 28, Issue 1, pp. 962–969). Elsevier B.V. https://doi.org/10.1016/j.sjbs.2020.11.007

Sumadewi, K. T., Harkitasari, S., & Tjandra, D. C. (2023). Biomolecular mechanisms of epileptic seizures and epilepsy: a review. In *Acta Epileptologica* (Vol. 5, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s42494-023-00137-0

Verma, M., Lizama, B. N., & Chu, C. T. (2022). Excitotoxicity, calcium and mitochondria: a triad in synaptic neurodegeneration. In *Translational Neurodegeneration* (Vol. 11, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s40035-021-00278-7

Vidal, J. E., Rivero, R. L. M., de Sousa dos Santos, S., Guedes, B. F., Gomes, H. R., Penalva de Oliveira, A. C., & Garcia, H. H. (2022). Case Report: Calcified Cerebral Toxoplasmosis Associated with Perilesional Edema in People Living with HIV/AIDS: Case Series of a Presentation Mimicking Neurocysticercosis. *American Journal of Tropical Medicine and Hygiene*, *106*(5), 1426–1433. https://doi.org/10.4269/ajtmh.21-1175

Wahyuni, S. (2013). TOXOPLASMOSIS DALAM KEHAMILAN. *Urnal Litbang Pengendalian Penyakit Bersumber Binatang Banjarnegara*, *9*.

Wohlfert, E. A., Blader, I. J., & Wilson, E. H. (2017). Brains and Brawn: Toxoplasma Infections of the Central Nervous System and Skeletal Muscle. In *Trends in Parasitology* (Vol. 33, Issue 7, pp. 519–531). Elsevier Ltd. https://doi.org/10.1016/j.pt.2017.04.001