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Case Report

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Cat Scratch Disease and Psychotic Illness: Exploring a Potential Link

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Abstract

Cat scratch disease, a common bacterial infection caused by *Bartonella henselae*, typically presents mild, self-limiting symptoms. However, emerging evidence suggests a possible link between CSD and an increased risk of developing psychotic illnesses, such as schizophrenia. This narrative review examines the existing literature to explore this potential association. We discuss the epidemiology and pathogenesis of CSD, focusing on how *Bartonella henselae* can disseminate throughout the body and potentially impact the central nervous system. Potential mechanisms of neurotoxicity, including neuroinflammation, blood-brain barrier disruption, and molecular mimicry, are explored. We analyze serological studies and case reports that provide preliminary evidence for a connection between CSD and psychosis, while acknowledging the limitations of these studies in establishing causality. Furthermore, we broaden the scope to consider the concept of the "infectome" and the potential role of other infectious agents in mental illness. This review highlights the need for robust, longitudinal studies to clarify the relationship between CSD and psychotic disorders. Understanding this potential link has significant implications for public health awareness, preventive measures, and clinical vigilance in diagnosing and treating both CSD and psychotic illnesses.

Keywords: Cat scratch disease, Bartonella henselae, Psychotic disorders, Schizophrenia, Mental illness, Neuroinflammation, Blood-brain barrier, Molecular mimicry, Infectome

Introduction

Cat scratch disease (CSD) is a bacterial infection caused by Bartonella henselae. It is typically transmitted to humans through a scratch, lick, or bite from cats, especially kittens. Cat fleas are responsible for horizontal transmission of the disease from cat to cat, and on occasion, arthropod vectors (fleas or ticks) may transmit the disease to humans [1].

The disease typically causes a mild illness in immunocompetent hosts. The clinical hallmark is lymphadenopathy at the site of inoculation. In the immunocompetent host, a granulomatous response ensues. The immunocompromised host may develop a vascular-proliferative response. The disease can disseminate to the eye, liver, spleen, and central nervous system [2]. CSD is also the most common cause of infectious lymphadenitis in children, adolescents, and young adults [3]. Psychosis refers to a collection of symptoms that affect the mind, where there has been some loss of contact with reality. During an episode of psychosis, a person's thoughts and perceptions are disrupted and they may have difficulty recognizing what is real and what is not. Studies estimate that between 15 and 100 people out of 100,000 develop

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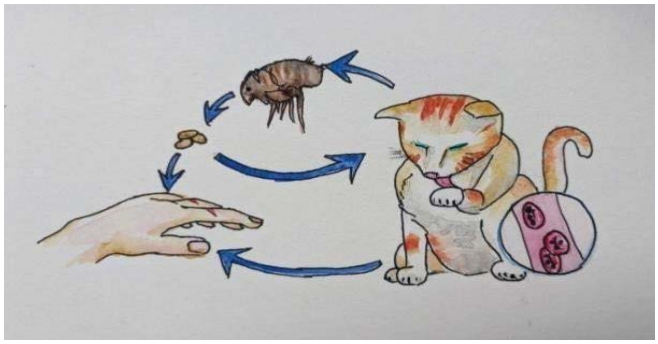
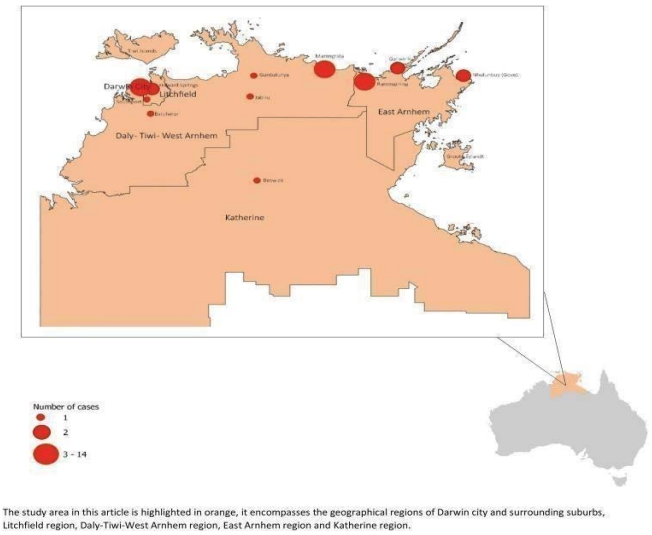


Figure 1: Transmission of Bartonella. Mammalian intra-erythrocytic bacteremia leads to bacterial presence in the flea digestive tract following a blood meal. The contaminated flea feces then lead to infection in humans and animals, which can be facilitated by animal scratches or licking [52].

psychosis each year [4] Among these, schizophrenia stands out as a prominent example. Schizophrenia is characterized by positive psychotic symptoms such as hallucinations, delusions, disorganized speech, and disorganized or catatonic behavior; negative symptoms such as reduced motivation and expressiveness; and cognitive impairments affecting executive function, memory, and mental processing speed [5]. This review aims to explore scientific literature to determine whether there is a credible association between Cat Scratch Disease and an increased risk of psychotic illnesses. A new study has found that patients diagnosed with schizophrenia, or another psychotic disorder are three times more likely to have Bartonella DNA in their blood than adults without these disorders [6].

Figure 2: Forty-three percent of participants diagnosed with psychosis had Bartonella DNA in their blood compared to 14% in the control population [23].

Cat scratch disease (CSD) has been found worldwide but is most prevalent in temperate climates. More than one-half occur in September through January in the United States. Seasonally, there is a notable increase in CSD cases during late summer and fall. This trend is thought to correspond with flea activity, which peaks during these warmer months, thereby increasing the transmission of *B. henselae* among cats and subsequently to humans [7]. The incidence of cat-scratch disease was reported to be 6.4 cases per 100,000 population in adults and 9.4 cases per 100,000 population in children aged 5-9 years globally [8].



The study area in this article is highlighted in orange, it encompasses the geographical regions of Darwin city and surrounding suburbs, Litchfield region, Daly-Tiwi-West Arnhem region, East Arnhem region and Katherine region.

Figure 3: Geographical distribution of Bartonella infections in the Top End from 2005 to 2019 [9].

Bartonella species primarily affects animals, with humans often infected incidentally. Of the 20 or more described species, three species are responsible for the vast majority of human bartonellosis. This includes Bartonella henselae—a globally endemic slow fastidious Gram-negative Bacillus typically associated with self-limited regional lymphadenopathy (cat scratch disease (CSD) [9].

The bacterium is transmitted to cats through fleas. After infection, the bacteria colonize the feline bloodstream, where they can remain asymptomatic in the host. When a human is scratched or bitten by an infected cat, *B. henselae* can enter the human bloodstream [10]. Once inside the body, *Bartonella* targets CD34+ cells which are specialized white blood cells that act as precursors for endothelial cells which are cells that line blood vessels and other tissues. After it enters into the cell, it prevents the cell from self-destructing

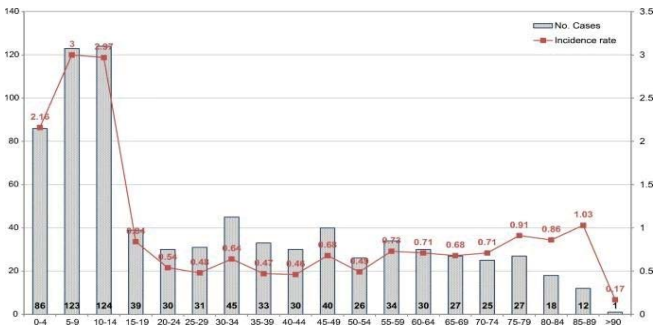


Figure 4: Epidemiology of Cat Scratch Disease among inpatients in the Spanish Health Care system [53].

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and also creates a vacuole, a protective cyst around itself. An endotoxin called lipid A which is commonly found in the outer membrane of gram-negative bacteria is the primary virulence factor for Bartonella. The ability of the organism to invade erythrocytes and endothelial cells plays a major role in the pathogenesis of the disease process. The organism alters the immune system in such a way that makes the host susceptible to infections by other bacterial pathogens. After this acute phase, the organism invades the endovascular, lymphatic, and other organ systems of the body contributing to multiple presentations of the disease.[11]

The diagnostic modalities commonly used in the diagnosis of *Bartonella* infection include serological testing, culture, histopathology, and polymerase chain reaction. There are five blood tests available: Western blot, ELISA, IFA tests, PCR DNA detection, and culture. However, it must be emphasized that *Bartonella* often is only intermittently present in the peripheral blood (bacteremia) of infected animals.

Direct Detection Methods

1. Isolation in culture.
2. Detection of antigens of the pathogen.
3. PCR- detection of nucleic acid (DNA).
4. Visualization by special stains.

Indirect Detection Methods

1. Serology - detection of antibodies against pathogens.
2. Detection of an immune cellular response against the pathogen- Bartonella skin tests. No longer used [8].

Unfortunately, a gold standard for definitive diagnosis of CSD has yet to be established [12]. Concerns about the serologic diagnosis of CSD include the use of low titers for positivity, incomplete diagnostic evaluation, and the lack of convalescent serologic testing. We propose a clinical guide to assist in managing suspected cases of CSD [13]. Treatment depends on the severity of the disease. In healthy individuals, CSD is usually self-limiting, and no specific treatment may be required. Azithromycin and rifampin are typically used as the first-line treatment for local manifestations of Bartonella infections, and doxycycline and gentamicin are used to treat trench fever, chronic bacteremia, and endocarditis [14]. Often, with serious infections, more than one antibiotic is used [15]. For persistent and severe infections such as B. henselae infections, one drug is not enough, and a drug combination approach is needed [15].

III The Brain Under Siege: How Bartonella henselae Might Impact the Central Nervous System

Usually, Cat Scratch Disease manifests with localized symptoms. However, in some cases, Bartonella colonizes endothelial cells (ECs), enters the bloodstream, and infects erythrocytes [2]. The bacteria's preference for endothelial cells (which line blood vessels, including those in the brain) gives it the potential to reach the central nervous system, setting the stage for neurological involvement.

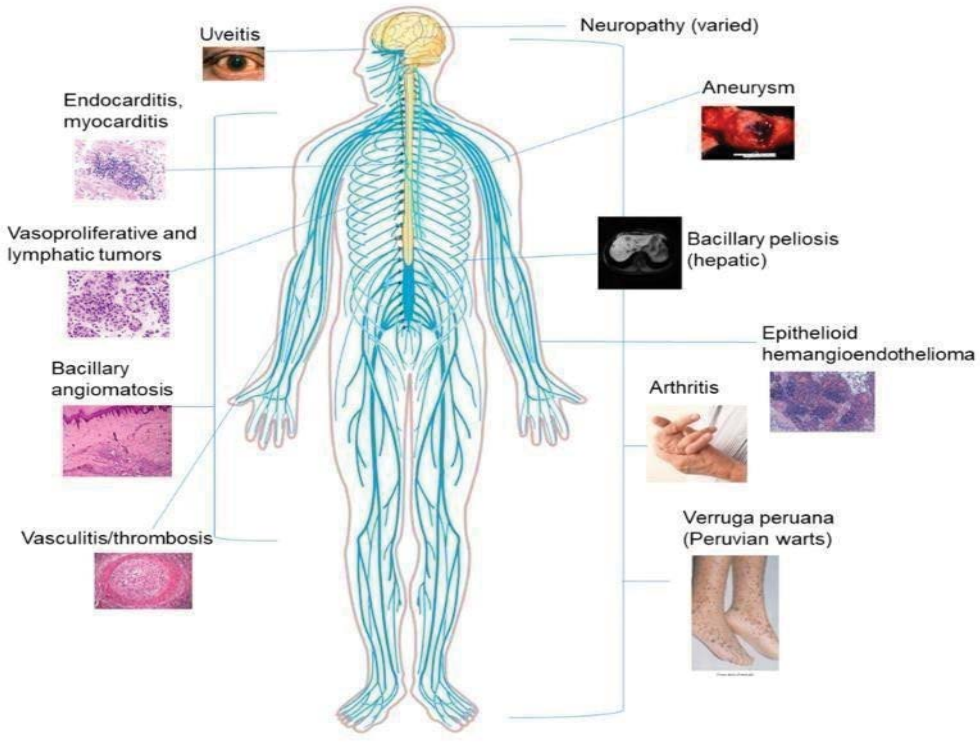

Figure 5: The clinical manifestations of human Bartonellosis [10].

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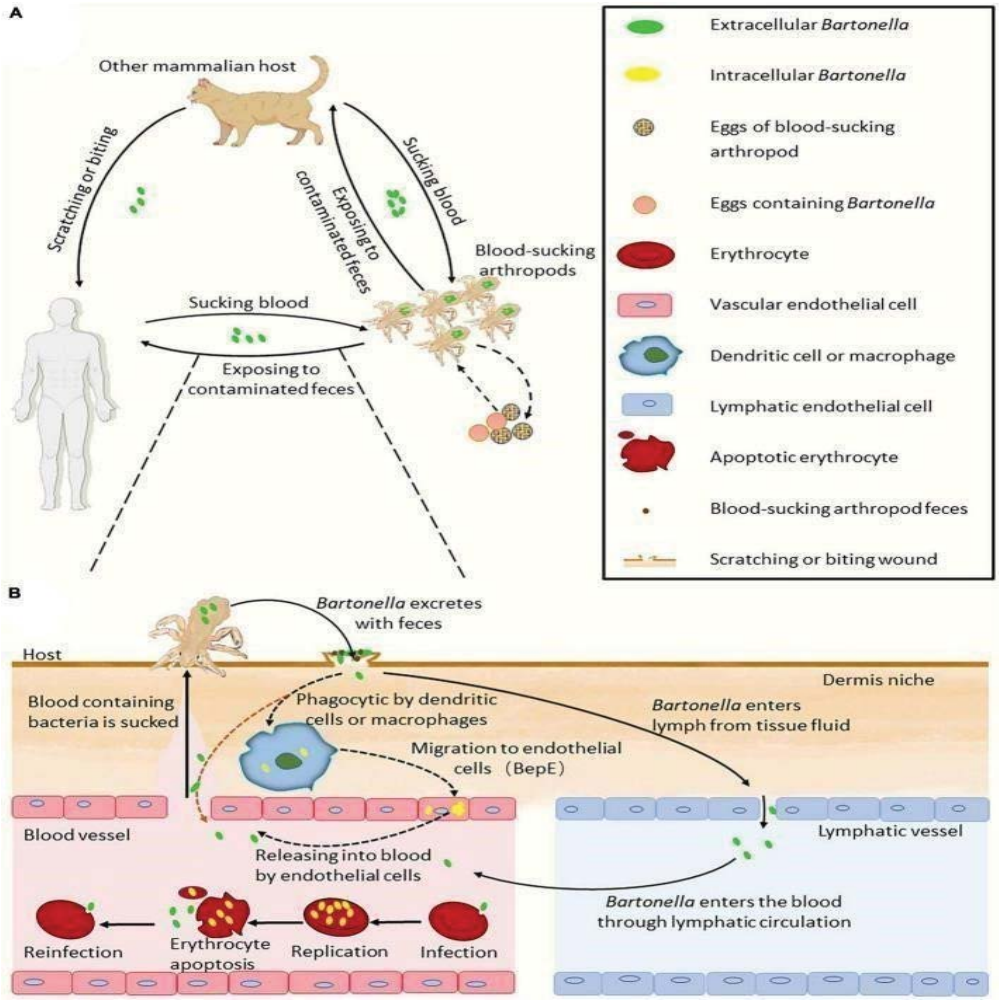

Figure 6: Model of *Bartonella* infection cycle. **(A)** The process of *Bartonella* transmission in the hosts. **(B)** The ways Bartonellae enter the blood. There are two ways for Bartonellae with VirB/VirD4 T4SS enter the blood. The first way may be through the host's macrophages, endothelial cells and other migration into the blood. The second way is through lymphatic circulation into the blood. Bartonellae absent of VirB/VirD4 T4SS, such as *B. bacilliformis*, may enter the blood with feces directly through the wound bitten by sand flies (the orange dashed line arrow). In the figure, the solid line arrow indicates the confirmed process, and the dashed line arrow indicates conjecture. Some elements in the figure were drawn by Fig Draw [20].

Central nervous system manifestations of Bartonella species are rare and include meningitis, neuroretinitis, encephalitis, and isolated optic neuritis [16]. It can trigger inflammation in the brain and can lead to damage when it occurs within delicate neural tissues, potentially causing psychiatric symptoms like hallucinations, cognitive dysfunction, and mood disturbances [17]. The blood-brain barrier (BBB) is a natural protective membrane that prevents the central nervous system (CNS) from toxins and pathogens in blood. [18] it acts as a selective filter, protecting the brain from harmful substances in the bloodstream. The concept of molecular mimicry describes situations in which antigen sharing between parasites and hosts could benefit pathogen evasion from host immune responses [19]. When the immune system identifies B. henselae as a threat, it produces antibodies and immune cells that not only target the bacteria but also cross-react with these similar brain proteins. In the context of Bartonella henselae, the bacterium might produce proteins similar to those found in the brain, like myelin or neural receptor proteins.[20] The immune response initially aims to target B. henselae, but due to the resemblance, it may also attack these brain-related proteins, resulting in autoimmune damage.[14] This cross-reactivity could potentially cause neuroinflammation and neuronal injury, leading to psychiatric manifestations like hallucinations, cognitive disturbances, or even psychosis.[21] Several case studies and reviews suggest that some patients with chronic B. henselae infections present with neuropsychiatric symptoms that improve with targeted antibiotic therapy, highlighting the role of infection in psychiatric conditions via mechanisms like molecular mimicry.

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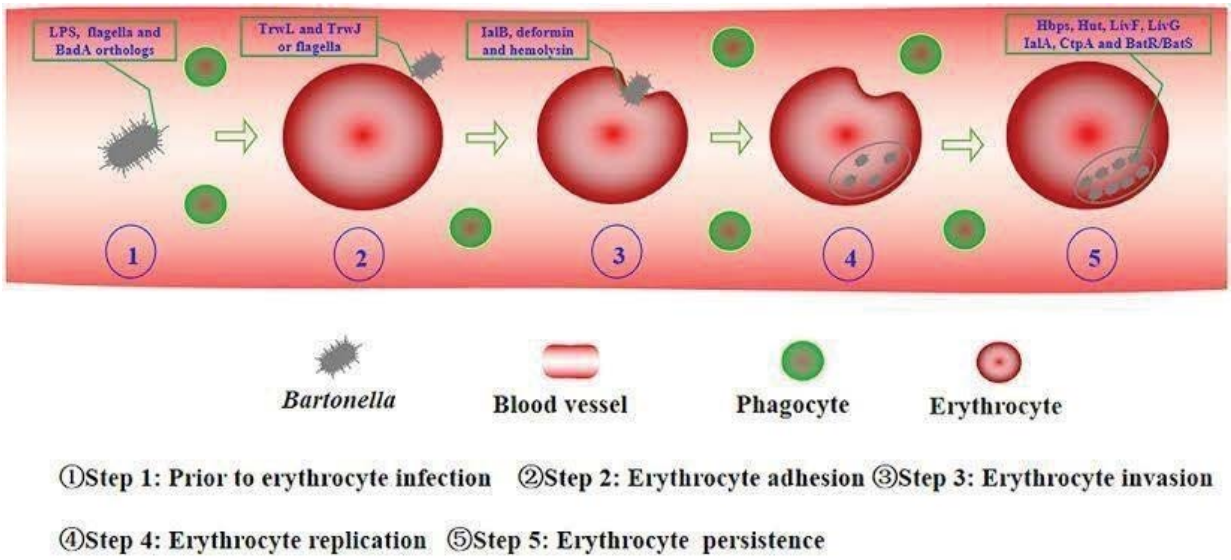

Figure 7: Holistic view of *Bartonella* interactions with erythrocytes. Before erythrocyte infection, *Bartonella* must escape the host immune responses to facilitate their extracellular longevity to approach and infect erythrocytes efficiently. *Bartonella* uses LPS, flagella, and BadA orthologs against phagocytes and complement activation [54].

IV: The Evidence: Connecting the Dots Between CSD and Psychotic Illness Serological Studies:

Serological studies have sought to determine whether individuals with psychotic disorders, such as schizophrenia, have a higher prevalence of antibodies against Bartonella henselae compared to healthy controls. Some studies have reported elevated levels of B. henselae antibodies in patients with schizophrenia, suggesting a potential link between exposure to the bacterium and the development of psychotic symptoms. A study found that patients with severe mental illness, including schizophrenia, had a higher prevalence of antibodies to B. henselae than nonpsychiatric controls [22] Moreover a study showed that up to 29% of individuals with severe mental illness tested positive for B. henselae antibodies compared to only 7% of healthy controls.[14] One more study reported significantly elevated C-reactive protein CRP) levels and interleukin 6 (IL-6) in the psychosis group compared to the controls unaffected by psychosis [23].

Case Reports

Case 1

A 15-year-old female developed psychotic symptoms, including delusions and hallucinations, approximately three weeks after the onset of CSD, characterized by fever and lymphadenopathy [24]. She required hospitalization, and treatment with antibiotics and antipsychotics led to significant improvement in both the infection and psychiatric symptoms [24]. This case suggests a possible direct or inflammatory effect of Bartonella henselae on the central nervous system [25].

Case 2

A 40-year-old male with a history of mild depression experienced an acute psychotic episode, including disorganized thinking and severe agitation, a month after being diagnosed with CSD [26]. The psychotic symptoms improved with antibiotics and antipsychotics, highlighting how CSD might exacerbate pre-existing psychiatric conditions [27].

Case 3

A 25-year-old female with CSD presented with both psychotic symptoms (delusions and hallucinations) and neurological symptoms (confusion and altered mental status) [28]. Treatment with antibiotics, antipsychotics, and neurological support led to substantial recovery with no long-term effects (6). This case underscores the need for a multidisciplinary approach in managing both psychiatric and neurological symptoms associated with CSD [29].

These case reports highlight the importance of considering CSD in patients presenting with acute psychosis, particularly if there is a history of cat exposure [30]. Early and effective treatment with antibiotics targeting Bartonella henselae and supportive psychiatric care is crucial for managing these cases [31]. A multidisciplinary approach is often required to address both the infectious and psychiatric components of the illness [32].

V. Other Infectious Suspects: Broadening the Scope

Schizophrenia is a multifactorial mental disorder with a complex etiology involving genetic, neurobiological, and environmental factors [33] Its development is

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Patient Age (years)/ Gender	Negative laboratory results	Positive laboratory results	Ocular imaging	Other imaging
1 29/Female	CSD, PPD; Syphilis, Lyme disease, and Toxoplasma serology, *Bartonella henselae* IgM	*Bartonella henselae* IgG (1:320), ESH: 20 mm/hr	Early hypo-, late hyperfluorescent lesion under the right ST vessel arcade OCT: Right CME and subretinal fluid	-
2 10/Female	TSD, CRP, ESR; Toxoplasma and Brusella serology, Quantiferon, Anti-NMO IgG, *Bartonella henselae* IgG	*Bartonella henselae* IgM	Visual field: Not reliable Retinal nerve fiber layer analysis: Thinning in the left superior quadrant	Cranial MRI: N Orbital MRI: Left optic nerve widening and enhancement Paranasal sinus CT: Sinusitis Chest X-ray: N
3 27/Male	CSD, Hepatitis and syphilis serology, ESR	*T. gondii* IgG, Anti-Hbs, Rubella IgG, Cytomegalovirus IgG, CRP, *Bartonella henselae* IgM (1:100) and IgG (1:320)	FA: Right IT infiltrates show central hypofluorescent surrounded by hyperfluorescent staining, delayed IT arteriolar filling and IT vein wall staining Heavy fluorescein leakage from the left OD, early hypo-, late hyperfluorescent juxtapapillary infiltrate Visual field: Bilateral generalized depression	Cranial MRI: N Orbital MRI: N
4 54/Female	CSD, PPD; Syphilis, ACE, Lysozyme, CRP	*Bartonella henselae* IgM (1:100) and IgG (1:320), ESR: 90 mm/hr,	FA: Focal staining of right/left optic disc, PP retinal infiltrates showing central hypofluorescence and surrounding hyperfluorescence located in and around the temporal vascular arcades Right SN arteriole filling delay Visual field: Right IT quadrantanopsia	Chest X-ray: N
5 16/Male	CSD, ESR, CRP	*Bartonella henselae* IgG	FA: Hyperfluorescence foci in the ST and IN of right eye; sheathing of the veins returning from the OD, SN branch retinal artery occlusion, vascular leakage in temporal periphery in left eye, Visual field: Left IT quadrantanopsia	-
6 41/Female	CSD, CRP, ESR; Toxoplasma, Syphilis, Hepatitis B and C serology, Quantiferon, anti-Aquaporin 4	*Bartonella henselae* IgM (1:100) and IgG (1:320), Homocysteine	FA: Left OD staining, early and late hyperfluorescent soft exudates in the nasal OD	Cranial MRI: N
7 12/Female	CSD, PPD; Syphilis, Toxocara, Lyme disease, and Toxoplasma serology; ACE, Lysozyme, Peripheral spread	*Bartonella henselae* IgM (1:100) and IgG (1:320), ESR: 25 mm/hr, CRP	-	Chest CT: N
8 16/Female	CSD, PPD; Syphilis, Toxocara, Lyme disease, and Toxoplasma serology, *Bartonella henselae* IgM	*Bartonella henselae* IgG	Visual field: Enlarged blind spot in the left eye	-
9 6/Female	CSD, peripheral spread, ACE, lysozome, PPD, cytomegalovirus serology, *Bartonella henselae* IgM	*Bartonella henselae* IgG, ESR: 25 mm/hr, CRP	Orbital USG: Punctate opacities and choroidal thickening in the vitreous of the left eye	Chest CT: N Orbital MRI: Enhancement around the left ciliary body and along the choroid
10 58/Male	CSD, PPD; Syphilis, Toxocara, Lyme disease, and Toxoplasma serology; ACE, Lysozyme, Peripheral spread	*Bartonella henselae* IgM and IgG, ESR: 68 mm/hr, CRP	OCT: Left central macular thickening and serous retinal detachment	Chest CT: N OCT: PP subretinal fluid

Figure 8: Laboratory findings and imaging results at presentation in patients with ocular involvement of cat scratch disease [55].

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Signs – symptoms	No	%
Fever	40	71,4
Lymphadenopathy	43	76,8
Neck	20	35,7
Inguinal	11	19,6
Armpit	12	21,4
Hepato-splenomegaly	7	12,5
Arthalgia	5	8,9
Malaise	5	8,9
Rash	5	8,9
Maculopapular	1	1,8
Papular	1	1,8
Erythema nodosum	2	3,6
Headache	4	7,1
Impaired vision (vision loss, squint)	8	14,3
Myalgia	2	3,6
Anorexia	3	5,3
Vomiting	2	3,6
Pericarditis	2	3,8
Arrhythmias	5	8,9
Confusion, loss of conscience	6	10,7
Hematuria	2	3,5
Stiff neck	2	3,6

Figure 9: Signs And Symptoms Recorded among 56 confirmed cases of cat scratch disease [56].

influenced by a combination of hereditary predispositions, neurodevelopmental abnormalities, and psychosocial stressors [34] This complexity makes it difficult to isolate the effects of a single factor, such as an infection, on the onset of schizophrenia. Infections like CSD can manifest differently across individuals, with varying degrees of severity and diverse symptomatic profiles [35]. While some individuals may experience neuropsychiatric symptoms, others may not. This variability complicates the task of linking CSD directly to the development of a complex disorder like schizophrenia. Largescale cohort studies involving diverse populations can help identify and validate associations between CSD and schizophrenia. These studies should include a substantial sample size to ensure statistical power and generalizability of findings [36]. By comparing individuals with and without CSD and tracking their mental health outcomes over time, researchers can better isolate the impact of the infection. confounding factors can obscure the relationship between CSD and schizophrenia. These include:

1) Genetic factors play a significant role in schizophrenia, and distinguishing the impact of an infection from underlying genetic vulnerabilities is difficult [37].
2) Environmental stressors, such as childhood trauma, substance abuse, or socioeconomic factors, can influence the risk of developing schizophrenia and may interact with infection-related factors [38].

The concept of the "infectome" refers to the comprehensive collection of microorganisms—including bacteria, viruses, fungi, and parasites—that an individual has been exposed to throughout their lifetime.[39]

This concept extends beyond the mere presence of infections to encompass the entire spectrum of microbial interactions an individual encounters, including transient exposures, chronic infections, and the influence of these microorganisms on host health [40]. The gut microbiome, a critical component of the infectome, plays a crucial role in metabolic processes, immune system regulation, and even neurological functions. Disruptions to the microbiome have been linked to various health issues, including mental disorders [41] The gut-brain axis, the bidirectional communication between the gut microbiome and the brain, is a significant area of research. Disruptions in the microbiome have been implicated in neurodevelopmental disorders and mental health conditions, highlighting the potential impact of the infectome on mental health from early life [42].

V. Conclusion and Future Directions

Bartonella henselae may impact the brain through mechanisms such as direct infection of the central nervous system, inflammatory responses, and interactions with neuroimmune pathways [43]. These processes could potentially lead to psychiatric symptoms, including psychosis. The current data primarily indicates a potential association,

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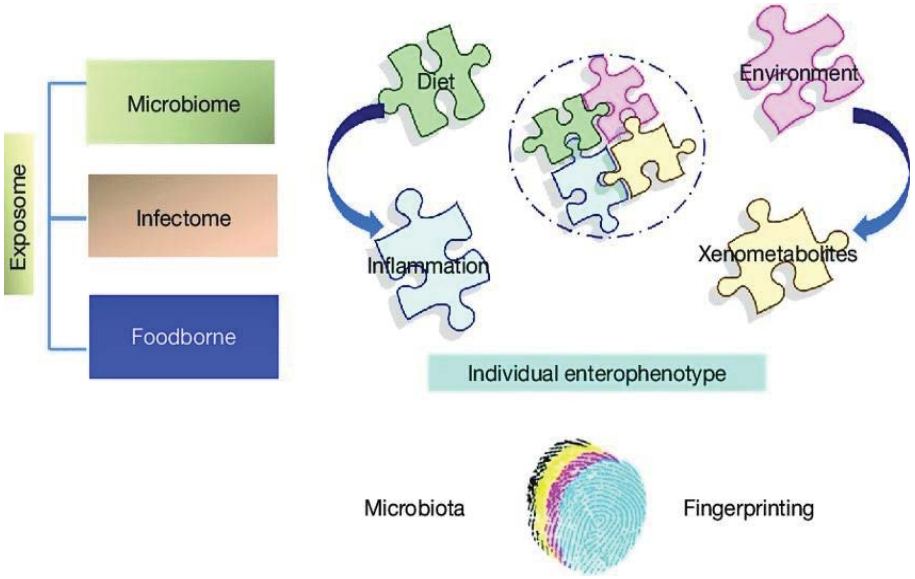

Figure 10: Exposome variables and individual microbiota enterophenotypes [57].

necessitating further research to determine if CSD directly contributes to the development of psychotic disorders or if other factors are at play [50].

To better understand the relationship between CSD and psychotic illness, several research directions are needed: -

1) Large-scale, prospective, longitudinal studies are essential to clarify this relationship. Such studies should follow individuals diagnosed with CSD over extended periods to assess their risk of developing psychosis compared to control groups without CSD [44].

2) Future research should identify genetic or environmental factors that might modify the risk of developing psychosis following CSD. Understanding how these factors interact with the infectome could provide insights into why some individuals are more susceptible [45]

3) Investigating the potential long-term effects of Bartonella henselae infection on the brain, even in individuals who do not develop overt psychosis, is crucial. This research could reveal subclinical effects or predispositions that might influence mental health later in life [46].

Implications for Public Health and Clinical Practice

1) Educating the public about the risks and preventive measures is essential for reducing the incidence of CSD and associated complications [47].

2) Preventive strategies include practicing good hygiene, such as thoroughly washing hands after handling cats, and avoiding rough play that could lead to scratches or bites. Prompt medical attention for any cat scratches or bites, especially if signs of infection appear, is also crucial [48].

Clinical Vigilance

1) Clinicians should consider CSD as a potential differential diagnosis in patients presenting with psychiatric symptoms, particularly if there is a history of cat contact. Awareness of this potential link can aid in more accurate diagnosis and treatment [49].

2) Early diagnosis and treatment of CSD might mitigate potential long-term neurological consequences. Prompt intervention may help prevent the progression of symptoms and reduce the risk of developing psychotic disorders [50]

3) Further research should explore the benefits of specific treatments for Bartonella henselae infection, particularly in individuals at high risk of psychosis, such as those with a family history of mental illness. [51]

Final Remarks

While the potential link between cat scratch disease and psychotic illness is an emerging area of research, current evidence suggests a compelling need for further investigation. Although typically presenting with mild, self-limiting symptoms, CSD, caused by the bacterium *Bartonella henselae*, has the potential to impact the central nervous system through mechanisms like neuroinflammation and blood-brain barrier disruption. Serological studies and case reports have revealed a possible association between CSD and the development of psychotic disorders, including schizophrenia. However, robust, longitudinal studies are crucial to establish causality and determine the true extent of this risk. Understanding the complex interplay between *Bartonella henselae* infection and mental health has significant implications for public health awareness, preventive measures, and clinical vigilance in

diagnosing and treating both CSD and psychotic illnesses. Further research in this area holds promise for developing novel strategies for prevention, early intervention, and treatment, ultimately improving the lives of individuals affected by these debilitating conditions.

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