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Prolonged Febrile Illness Due to Brucellosis in a Child with Autism Spectrum Disorder, Thalassemia Minor and Vitamin D deficiency: A diagnostic Challenge

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Abstract

Background: Brucellosis is a zoonotic infection with protean manifestations and remains under diagnosed in children, especially when presenting as a prolonged fever without focus. Co-morbid neurodevelopmental disorders and haemoglobinopathies may further complicate evaluation.

Case Presentation: We report a 6 year old boy with autism spectrum disorder, thalassemia minor and vitamin D deficiency, who presented with intermittent high-grade fever, nocturnal limb pain, abdominal discomfort, and hepato-splenic involvement. Extensive evaluation for common tropical and infectious causes was negative. Serology revealed Brucella Immunoglobulin M (IgM) positivity, while blood cultures remained sterile and Brucella polymerase chain reaction (PCR) was negative. The child responded clinically to oral rifampicin and co-trimoxazole therapy, though the course was complicated by intermittent fever recurrence and drug-related cutaneous reactions.

Conclusion: This case highlights the importance of considering brucellosis in children with prolonged fever, even in the absence of classical exposure history or positive cultures. Early recognition and appropriate antimicrobial therapy are crucial to prevent complications.

Key words: Brucellosis, Paediatrics, Prolonged fever, Autism spectrum disorder, Thalassemia minor, Vitamin D deficiency

1. Introduction

Brucellosis is a common zoonotic infection worldwide, particularly in endemic regions such as the Indian sub-continent. It is caused by Brucella species, especially Brucella melitensis and Brucella abortus, which are endemic across India due to its large agricultural and livestock population. In India, human brucellosis is reported from nearly all states and remains an important and under-recognized public health problem[1, 2]. The main mode of transmission is the consumption of unpasteurised dairy products [3]. Infection can

be contracted through direct contact with infected animals and there have been reported instances of acquiring disease following interactions with wild life [4]. Paediatric brucellosis often presents with non-specific symptoms including fever, arthralgia, abdominal pain and malaise, leading to frequent diagnostic delays. Blood cultures have limited sensitivity, and serology remains the cornerstone of diagnosis. We report a diagnostically challenging case of paediatric brucellosis in a child with autism spectrum disorder (ASD) and thalassemia minor, emphasizing the need for heightened clinical suspicion.

Case Presentation

A 6-year-old boy presented to our outpatient department with a history of fever for three days, with temperatures ranging from 100^{o}F to 102^{o}F, associated with nocturnal leg pain. Physical examination was unremarkable. He was initially managed symptomatically with antipyretics for a presumed viral illness, as several classmates were reportedly febrile.

On the fourth day of illness, because no focus of infection was identified, baseline investigations were performed. He returned the following day with persistent fever, leg pain, mild cough, and an elevated C-reactive protein (CRP) level of 2.1mg/dL (normal <0.5mg/dL). General and systemic examination remained normal. Oral cefixime was initiated for possible early sepsis or bacteremia while awaiting blood culture results.

By the seventh day of illness, he developed high-grade intermittent fever reaching 101.5^{o}F, predominantly in the evenings, accompanied by leg pain, and occasional cough. He also reported increased urinary frequency (>8 times/day) with out dysuria or other urinary symptoms. A blister was noted on the inner aspect of the left upper lip. Laboratory evaluation revealed vitamin D deficiency (13.8ng/ml), while serological tests for malaria, dengue and typhoid were negative.

The child was the only offspring of non-consanguineous parents and was delivered by caesarean section at term with an uneventful perinatal period. Immunizations were up to date. He had been diagnosed with Autism Spectrum Disorder at one year of age and was receiving speech and behavioural therapies. He also had a history of thalassemia minor and iron deficiency anaemia, for which he had received iron and folic acid supplementation.

Tonsillo-adenoidectomy had been performed in February 2025 for adenotonsillar hypertrophy associated with snoring and sleep apnoea. He had previously been hospitalized for recurrent Escherichia coli urinary tract infections. During a previous episode of prolonged fever with no identifiable source, he had shown improvement following empirical doxycycline therapy. One month before the current illness, he had visited a zoological park during a school excursion.

In view of persistent fever, he was admitted for further evaluation. Intravenous ceftriaxone was initiated for presumed sepsis. During hospitalization, he developed recurrent temperature spikes ranging from 101^{o}F to 102^{o}F associated with chills and rigors. Blood cultures obtained on admission showed no bacterial growth, and ceftriaxone was discontinued. Given the persistent fever and pending investigations, a three-day course of azithromycin was administered to cover atypical infections including Mycoplasma, Chlamydia, and Lyme disease.

Ultrasonography of the abdomen revealed increased periportal echogenicity fo the liver (starry-sky appearance) and mild splenomegaly. Repeat blood cultures could not be obtained because of difficult

venous access. Liver and renal function tests were normal. Serological testing for chikungunya, dengue, typhoid, leptospirosis, Epstein-Bar virus, mycoplasma and scrub typhus was negative.

The CRP level initially increased to 2.7mg/dL but subsequently improved. On day 11 of illness, Brucella IgM enzyme-linked immunosorbent assay (ELISA) was reported positive. Extended blood cultures were subsequently sent and remained negative after 21 days of incubation.

The chronological investigations are enumerated in Table 1, 2, 3 and 4.

Table 1. Haematological and Inflammatory Investigations

Parameter	22-09-2025	25-09-202	27-09-2025	Reference Range
CRP (mg/dL)	2.1	2.7	2.1	<0.5
Hemoglobin (g/dL)	9.7	9.8	9.1	12–15
RBC (mil/cmm)	5.42	5.55	5.08	3.8–4.8
PCV (%)	29.2	29.7	26.9	36–46
MCV (fL)	53.9	53.5	52.8	83–101
MCH (pg)	17.8	17.6	17.9	27–32
MCHC (%)	33.1	32.8	34.0	31.5–34.5
RDW-CV (%)	18.1	17.4	16.9	11.6–14
Eosinophils (%)	4	4	5	1–6
Monocytes (%)	8	8	8	2–10
Basophils (%)	0	0	0	0–2
Platelet Count (lakhs/cmm)	2.75	4.08	5.01	1.5–4.1
MPV (fL)	7.7	9.0	8.9	7–10
PDW (%)	13.0	12.3	11.9	9–14
WBC (cells/cu.mm)	5200	4400	5500	4000–10000
Neutrophils (%)	50	56	52	40–80
Lymphocytes (%)	38	32	35	20–40

Table 2. Infectious Disease Evaluation

Investigation	Result
Dengue NS1 Antigen	Negative
Dengue IgM Antibody	Negative
Typhidot IgM	Negative
Typhidot IgG	Negative
Malarial Parasite	Negative
Chikungunya IgM	Negative
Chikungunya IgG	Negative
Leptospira IgM	Negative
CMV IgG	Negative
CMV IgM	Negative
Scrub Typhus IgM	Negative

EBV VCA IgG	Negative
EBV VCA IgM	Negative
QuantiFERON-TB Gold	Negative
Mantoux Test	<5 mm induration
Mycoplasma pneumoniae IgM	Negative
Brucella IgM Antibody	Positive
Brucella PCR	Negative

Table 3. Biochemical, Urine and Microbiological Investigations

Investigation	**Result**	**Reference Range**
Total Bilirubin (mg/dL)	0.24	0.2–1.3
Direct Bilirubin (mg/dL)	0.09	0–0.2
Indirect Bilirubin (mg/dL)	0.15	0–1.1
Total Protein (g/dL)	8.3	6.4–8.2
Albumin (g/dL)	4.7	3.5–5
Globulin (g/dL)	3.6	1.8–3.6
AST/SGOT (U/L)	34	17–59
ALT/SGPT (U/L)	20	13–69
GGT (U/L)	20	15–73
Alkaline Phosphatase (U/L)	162	38–126
Blood Urea (mg/dL)	21	19–43
Serum Creatinine (mg/dL)	0.40	0.66–1.25
Serum Uric Acid (mg/dL)	3.5	3.5–8.5
Random Blood Sugar (mg/dL)	81	70–140
Serum Sodium (mmol/L)	137	137–145
Serum Potassium (mmol/L)	5.0	3.5–5.1
Serum Chloride (mmol/L)	98	98–107
LDH (U/L)	485	—
Vitamin D (ng/mL)	13.85	Insufficient
Urine Analysis	Normal	—
Blood Culture	No growth after 5 days	—

Table 4. Imaging Studies

Investigation	**Findings**
USG Abdomen & Pelvis (1)	Mild hepatosplenomegaly with nonspecific mesenteric lymphadenopathy
USG Abdomen & Pelvis (2)	Increased periportal echogenicity (“starry sky liver”) suggestive of acute viral hepatitis with mild splenomegaly
Echocardiography	Normal study
Chest X-ray (PA View)	Normal study

Based on the positive serology and current treatment recommendations, oral rifampicin (250 mg once daily) and co-trimoxazole (480/80 mg twice daily) were initiated for six weeks. The child demonstrated clinical improvement, with reduced frequency and intensity of fever spikes, and became afebrile within two days of therapy.

During follow-up on the ninth day of antibiotic treatment, he developed pruritus over the arms and elbows associated with dry skin and orange discolouration of urine attributable to rifampicin. He remained afebrile for seven days and was managed with emollients, calamine lotion, and cetirizine. The following day, he developed urticarial lesions over the left lower thigh and around the knee, which resolved with conservative management.

On day 13 of antibiotic therapy, he again developed low-grade fever (100-101^{o}F) for three days without rigors, requiring antipyretics once daily. Evaluation by immunologist and rheumatologist was sought because of breakthrough fever. Further investigations, including inflammatory markers, abdominal ultrasonography, and Brucella polymerase chain reaction (PCR), were recommended.

On day 20 of treatment, he experienced two episodes of fever (100^{o}F) approximately 15 hours apart, which responded to paracetamol. His appetite had improved significantly. However, he developed symptoms suggestive of viral illness, including coryza, abdominal discomfort, oral ulcers, and a generalized pruritic blanching erythematous macular rash involving the face, trunk, extremities, palms, and soles. Excessive sweating of the palms and soles was also reported. Examination revealed blanching erythematous macular rash with dermatographism. Differential diagnosis included a viral exanthem and drug-related eruption secondary to rifampicin or co-trimoxazole. The extended blood cultures remained negative for Brucella species. A Brucella PCR test performed independently by the family through a private laboratory on day 23 of antibiotic therapy was reported as normal. Repeat CRP and erythrocyte sedimentation rate (ESR) were within normal limits. Mild anaemia was noted with a haemoglobin concentration of 10g/dL.

Discussion

Brucellosis is a Zoonotic infection caused by Brucella species and remains an important yet under-recognised cause of prolonged fever in children in endemic regions such as South Asia. Paediatric brucellosis often presents with non-specific symptoms including fever, malaise, arthralgia, and hepatosplenomegaly, frequently leading to diagnostic delay and empirical diagnostic exposure before confirmation [5, 6]. In the present case, the child had persistent spiking fever with limb pains and abdominal discomfort without localizing signs, a typical but non-specific presentation reported in 70-90% of paediatric cases [7].

The epidemiological history of animal exposure is often subtle in children. Direct contact with live stock or consumption of unpasteurised dairy products are classic risk factors; however, indirect exposure during visits to farms, petting zoos, or zoological parks has also been documented [8]. The history of a recent zoo visit in this child therefore represents a plausible exposure source.

Diagnosis of brucellosis in children relies on a combination of clinical suspicion and laboratory confirmation. Blood culture remains the gold standard but has limited sensitivity (30- 70%) and requires prolonged incubation, particularly after prior antibiotic use [5, 9]. In this case, repeated and extended cultures were negative, likely due to preceding antimicrobial therapy and low-grade bacteremia, a

recognized limitation. Serology therefore plays a central role; detection of anti-Brucella IgM antibodies by ELISA has high sensitivity in acute disease and is widely used in endemic settings [10]. The positive Brucella IgM ELISA in the context of compatible clinical features and hepatosplenomegaly supported the diagnosis. Ultrasound findings of peri-portal echogenicity (starry-sky liver) and splenomegaly are reported in systemic brucellosis due to reticuloendothelial involvement [11].

An additional notable aspect of this case is the co-existence of thalassemia minor, autism spectrum disorder (ASD) and vitamin D deficiency. Children with haemoglobinopathies such as thalassemia major are known to have increased susceptibility to certain bacterial infections due to iron overload, altered macrophage function, and immune dysregulation [15]. However thalassemia trait (minor) is generally considered immunologically normal, and there is no established evidence that carriers have increased risk of brucellosis. Current literature on infections in thalassemia predominantly concerns transfusion-dependent disease, and reports of zoonotic infections such as brucellosis in thalassemia minor are lacking [15,16]. Therefore the co-existence in this child is most likely incidental rather than causal, although mild baseline anaemia from thalassemia trait may complicate interpretation of haematologic changes during infection.

Similarly the presence of ASD in this child does not have a known biological association with brucellosis. Autism is a neurodevelopmental condition with multifactorial genetic and environmental determinants, and infectious associations reported in the literature primarily concern prenatal or early-life viral exposures rather than acquired zoonoses in childhood [17]. Some studies have noted that children with ASD may experience delayed diagnosis of medical conditions due to communication difficulties or atypical symptom reporting, which can contribute to prolonged febrile illness before evaluation [18]. This factor may partly explain the repeated healthcare visits and empirical treatments prior to diagnosis in the present case. To date, no published studies have demonstrated increased susceptibility to Brucella infection in children with ASD.

Routine checking of vitamin D level (due to previously low vitamin D level) in this child showed deficiency. Literature review showed Vitamin D plays an immunomodulatory role in macrophage activation and intracellular pathogen clearance, mechanisms relevant to control of Brucella infection [19]. Observational paediatric studies from endemic regions report a higher prevalence of vitamin D deficiency among children with brucellosis compared with healthy controls [20]. Vitamin D deficiency may therefore increase susceptibility (as in our case), disease severity, or chronicity in paediatric brucellosis, although causality remains unproven [21, 22]. Recognition of this association supports considering vitamin D status assessment and correction as an adjunct in comprehensive management [19, 20], which concurs with in our case presentation and management.

Treatment of paediatric brucellosis requires combination therapy to prevent relapse. Current recommendations suggest Rifampicin plus trimethoprim-sulfamethoxazole (TMP-SMX) for atleast 6 weeks in children under 8 years, as doxycycline- based regimens are generally avoided in younger age groups [6, 12]. The child received Rifampicin and TMP-SMX fro 6 weeks with rapid defervescence, consistent with reported response rates exceeding 90% [7]. Breakthrough low-grade fever during therapy has been described and may reflect intercurrent viral illness, immune response to bacterial antigen

clearance, or drug reaction rather than treatment failure when inflammatory markers normalize [13]. In this case normalization of CRP / ESR and clinical well-being supported adequate therapeutic response. Cutaneous manifestations during therapy included pruritic and urticarial rashes. Hypersensitivity reactions are recognized adverse effects of both rifampicin and sulfonamides, occurring in up to 5-10% of paediatric recipients [14]. Mild rashes with out systemic features can be managed symptomatically while continuing therapy, as done here. The absence of relapse after completing of treatment further supports effective eradication.

Overall, this case illustrates several typical paediatric brucellosis challenges: non specific presentation, culture negative disease, reliance on serology, and favourable response to Rifampicin-TMP-SMX therapy. It also highlights that coexisting conditions such as thalassemia trait and ASD may complicate clinical interpretation or healthcare access but do not appear to confer specific susceptibility to brucellosis based on current evidence. Awareness of brucellosis in endemic regions remains essential to avoid delayed diagnosis and complications.

Conclusion

Paediatric brucellosis should be considered in children from endemic regions presenting with prolonged or recurrent fever and hepatosplenomegaly, even with out obvious live stock exposure. Coexisting conditions such as thalassemia minor or autism spectrum disorder do not appear to increase susceptibility but may influence clinical evaluation. However vitamin D deficiency may increase susceptibility to brucellosis, therefore it should be included in comprehensive management. Serology remains crucial when cultures are negative. Combination therapy with Rifampicin and TMP-SMX for 6 weeks is effective and well tolerated. Early recognition prevents complications and chronic disease.

Learning points

1. Brucellosis is an important cause of fever of unknown origin in children in endemic regions.
2. Exposure history may be indirect (e.g., zoo or animal contact) and should be actively sought.
3. Blood cultures are frequently negative; serological testing (IgM ELISA) is valuable for diagnosis.
4. Thalassemia minor and autism spectrum disorder have no proven biological association with brucellosis but may influence clinical assessment.
5. Assessment of vitamin D status and management in all children with prolonged fever especially brucellosis
6. Rifampicin plus trimethoprim-sulfamethoxazole for 6 weeks is recommended therapy in young children.
7. Mild rash or transient fever during treatment does not necessarily indicate treatment failure.

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Conflicts of Interest

There are no conflicts of interest

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Informed Consent
Consent was obtained from parents, both written and verbal

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