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Case Report

Chronic Relapsing Q Fever Endocarditis in a Child in Saudi Arabia. A Case Report and Review of the Literature

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Abstract

Introduction: Although chronic Q fever is rare in children, by far endocarditis is the most common syndrome of chronic Q fever. This is particularly so when there is preexisting congenital heart disease. Such cases do present diagnostic and therapeutic challenges.

Case Report: We present a case of relapsed chronic Q fever endocarditis in an 8-year-old boy with double outlet right ventricle corrected by Yasui (Norwood/Rastelli) procedure with right ventricle-pulmonary artery conduit (contegra valve) insertion. At around three years of age, and after 4 months of onset of fever of unknown origin including three months of investigation, and two times admission for IV antibiotics for culture negative endocarditis, the diagnosis of Q fever endocarditis was confirmed by serology, and treatment with Ciprofloxacin was given for 2 years. Later the patient developed conduit stenosis and contegra valve calcification. We restarted him on Ciprofloxacin for another 3 years, we also added Rifampicin, however his anti-*Coxiella* antibodies titers were still rising, along with transaminitis and development of hepatomegaly. At that stage, we thought this was because of presence of infected pulmonary artery conduit (foreign material). The patient was referred to cardiac surgery for removal of what we thought was the source for persistence of his high anti-*Coxiella* antibodies titers. The patient underwent open heart surgery and conduit replacement. But his titers were not going down as excepted, so we started him on Doxycycline as he was 8 years old, and discontinued Ciprofloxacin and Rifampicin. He responded well initially, but liver enzymes remained high. Therefore, we restarted Ciprofloxacin again in addition to Doxycycline, which were effective in normalizing his liver enzymes. Unfortunately, the patient developed drug intolerance to Ciprofloxacin, so we had to switch it to Rifampicin. Soon Rifampicin was stopped due to recurrence of transaminitis, and Doxycycline was continued as monotherapy. On latest follow up, towards his ninth birthday, the patient again having rising C. *burnetii* antibodies titers.

Conclusion: The clinical course of chronic Q fever endocarditis can be slow and indolent in nature, some with relapses and treatment failure. Looking into the literature, up to 50% of the time, relapse can occur even with prolonged therapy. This patient here received at least 5 years of treatment for chronic Q fever endocarditis. Despite this, the patient still has relapse. So, the question remains: for how long we should treat a patient post relapse.

Keywords: *Q Fever Endocarditis; Child; Coxiella burnetii*

Introduction

Q fever is a zoonotic disease caused by *Coxiella burnetii*, an obligate intracellular pathogen [1]. Humans usually get infected by inhaled contaminated aerosols of feces, urine, birth products, and milk from cattle, sheep and goats - the natural reservoirs of *C. burnetii* [1,2]. The fastidious nature of this organism and the difficulty to grow on culture make seroconversion diagnostic of Q fever [3]. There are various clinical phenotypes associated with *C. burnetii* infection [1]. Q fever can present in an acute form, with the majority of cases being asymptomatic [4] and some presenting with fever and multiorgan involvement, or manifest as chronic disease. Chronic Q fever can have a slow and indolent course, with chronic Q fever endocarditis being the most common syndrome [1].

A notable risk factor for the development of Q fever endocarditis is the presence of preexisting valvular heart disease [1]. Some authors report that the majority of pediatric Q fever endocarditis have been associated with congenital heart lesions [5-7]. In a review of 408 cases of Q fever endocarditis most patients had preexisting valvular heart disease, with 38% of those patients reported to have prosthetic valves [8]. Age also plays a role; children under 15 years of age were found to be five times less likely than adults to be diagnosed with symptomatic Q fever given comparable levels of exposure and seroconversion rates [9,10]. Specific serologic testing using indirect immunofluorescence technique is the mainstay for diagnosis [3].

In Saudi Arabia we found only few reported cases of Q fever endocarditis in children [5,11,12]. Here we present a case of chronic relapsing Q fever endocarditis in an 8-year old child diagnosed and treated in King Abdulaziz Medical City (KAMC)-Jeddah, Saudi Arabia. This patient had earlier multistage repair of congenital heart disease in our sister hospital, King Abdulaziz Medical City (KAMC)-Riyadh, Saudi Arabia. This is a very rare disease in children, and this case is considered to be the first at our institution.

Case Presentation

This is an 8 years old patient born with double outlet right ventricle, doubly committed ventricular septal defect and coarctation of aorta. At the age of 2 weeks he underwent pulmonary artery banding plus aortic arch repair. At the age of 8 months, Yasui (Norwood/Rastelli) procedure for biventricular repair was performed with right ventricle (RV)-pulmonary artery (PA) conduit - contegra valve insertion.

When he was 29-months old he was admitted for fever of unknown origin lasting for about one month. Examination findings showed a pansystolic murmur and splenomegaly. Blood and urine cultures were negative. Serology was negative for *Brucella*, *Hepatitis B virus*, *Hepatitis C virus, Cytomegalovirus*, *Epstein-Barr Virus* and *Toxoplasma*. Echocardiography detected vegetation on the mitral valve, and the diagnosis of probable culture negative infective endocarditis was made. The child received Vancomycin for 6 weeks and Gentamicin for 2 weeks, and the vegetation started to regress, and later became calcific.

Soon his fever recurred, so he was readmitted to rule out subacute bacterial endocarditis and started on Ceftazidime and Vancomycin. Q fever endocarditis was suspected given the persistently negative cultures, and Amikacin and Rifampicin were added. Serology testing for *C. burnetii* came back with IgG > 300, IgM positive, confirming the working diagnosis. So, Ceftazedime was switched to Ciprofloxacin 10 mg/kg/dose every 12 hrs. After 7 weeks of IV antibiotic therapy and resolution of fever, the patient was discharged on oral Ciprofloxacin as monotherapy. A repeat echocardiogram after three months reported no vegetations. Oral (PO) Ciprofloxacin was continued for a total duration of two years, and then stopped.

At the age of four years, balloon dilatation of RV-PA conduit was done as he developed pulmonary artery conduit calcification and stenosis. The patient also developed hepatomegaly with transaminitis, and rising *C. burnetii* titers IgG 1920+, therefore the impression was a relapsed Q fever, and Ciprofloxacin was restarted at 15 mg/kg/dose every 12 hrs to continue for three more years. Rifampicin was later added at a dose of 30 mg/kg every 24 hrs, to which he had issues with compliance, so the dose of Ciprofloxacin was increased to 20 mg/kg/dose every 12 hrs. Afterwards, his *Coxiella* titers were not going down as expected, so he was referred back again for surgery for removal of the infected conduit, in order to get rid of what we thought was the source of persistence of his *Coxiella* antibodies. At six years

of age he underwent an open-heart surgery and replacement of the artificial valve and prosthetic conduit. The operation was complicated by stroke and seizures requiring Levetiracetam. His liver enzymes started to come down but not back to normal.

After one year of treatment, serology titers started to increase again; IgG (Phase II) 1:64000+, IgM (Phase II) 1:4069+, IgM (Phase I) 1:16000+, IgG (Phase I) > 1:64000. Ciprofloxacin and Rifampicin were discontinued, and Doxycycline was given as monotherapy at a dose of 2 mg/kg/dose every 12 hrs. Initially he responded well to this new antibiotic and his *Coxiella* IgG titers dropped from 1:64000 down to 1:200 in three months. However, he still had persistently high transaminases despite being asymptomatic, deferring reintroduction of Rifampicin for combination therapy. Ciprofloxacin was resumed as the response to Doxycycline started to plateau, IgG (phase I) >1:16000+, IgM (Phase I) 1:1020, IgG (Phase II) 1:4100+, IgM (phase II) 1:16. Liver transaminases then began trending down to normalcy within 4 months. Unfortunately, the child developed drug intolerance to Ciprofloxacin**,** and we had to switch it to Rifampicin. Consequently, transaminases started to rise again and were persistently high. Rifampicin was thought to be the cause, and Hydroxychloroquine was considered as an alternative. It was contraindicated however as the patient was having a prolonged QT-interval. Nevertheless, Rifampicin was stopped, and the patient continued on Doxycycline as monotherapy.

Discussion and Conclusion

Q fever, which is an enzootic disease, can occur anywhere in the world. Infection mostly occurs by inhalation of aerosols, or vapors from dried contaminated animal secretions [10,13]. Although Q fever endocarditis is one of the known causes of culture negative endocarditis [14], Q fever endocarditis is considered rare in children [7,15,16] and is a fatal disease if left untreated [17]. The first case of chronic Q fever endocarditis in a child was reported by Robert W. A. Jones in 1980 in London [18]. In the literature there are only few case reports of Q fever endocarditis in children [7,16].

When obtaining the history there was no identifiable source of infection. However, the patient had history of travel to Basra, Iraq. We thought that the patient lived near a livestock or slaughterhouse there, the family however were unsure. We suspected an epidemiological link here since there were reports of reemergence of Q fever in Iraq among military personnel after 11 September 2001 [19]. Additionally, there are reports that describe an association between contegra valve, which is of bovine source, and *Coxiella* endocarditis infection [20]. And since cattle is a natural reservoir of *C. burnetii*, then this link seems plausible. Furthermore, this organism is capable of inducing persistent animal and human cell infections [21], making eradication of infection especially difficult [21,22].

The diagnosis is by serological means, using direct immunofluorescence techniques. Titers of both phase I and phase II are used to differentiate between acute and chronic cases. With chronic infections, a phase I anti-*Coxiella* titer of IgG > 800 is considered diagnostic [3]. Phase II antibody titers are used for diagnosis of acute infection, with titers of IgG > 200 and IgM > 50 being diagnostic [3]. Interestingly enough, the Duke criteria for diagnosing endocarditis recently included IgG antibody titers ≥ 800 as a major criterion and stands as enough evidence for commencing antimicrobial therapy [23].

Our patient was initially admitted as a case of pyrexia of unknown origin for one month. He was treated with broad spectrum IV antibiotics for 6 weeks for culture negative endocarditis. His final diagnosis of Q fever endocarditis was arrived at one month post discharge, that is 4 months since the beginning of his illness with three months of extensive workup. On reviewing the literature, there is usually some delay before diagnosing chronic Q fever endocarditis that varies depending on the clinical picture, a mean time of six to 12 months delay has been reported [2,14,24].

Despite appropriate treatment with Ciprofloxacin for 2 years and decreasing *Coxiella* titers, stenosis of conduit with a rise in phase I IgG titers to 1920+ marking his first relapse. This child had a relapsing remitting course with medication side effects necessitating switching antimicrobials several times. His illness was not straightforward, having complications of conduit vegetation and stenosis requiring removal. His second relapse was one year after the surgery despite taking appropriate antibiotics daily.

In the literature there is very little information describing relapse rates and the long-term treatment of relapsed Q fever endocarditis in children. Most reports described a 50% chance of relapse despite prolonged treatment [22,25]. Besides, there is no standard duration for treatment of chronic Q fever endocarditis, with few references mentioning a long duration of treatment between 3 years and a life-time [24,25]. Giving Doxycycline plus Rifampin for six months followed by Doxycycline alone was shown to be superior to Doxycycline monotherapy [26]. A 10-year survey done by Didier Rauolt., *et al*. in 1999 demonstrated that giving a combination of Doxycycline and Hydroxychloroquine for a minimum of 18 months, would improve the prognosis of Q fever endocarditis. This regimen can shorten the overall duration of therapy and limit the number relapses [24]. This study however did not include children. Million et al did a 26-year survey looking at factors predicting the outcome of Q-fever endocarditis. Factors found to be associated with serological failure were male sex, a high phase I IgG titer at the time of diagnosis, and a delayed starting of Hydroxychloroquine for treatment [22].

He concluded that the most effective treatment for chronic Q fever is a combination of Doxycycline and Hydroxychloroquine for at least 18-24 months, however a high risk of relapse persists even with prolonged treatment [22]. Current practice did not change however [27]. Alternative regimens like combining Doxycycline with a Quinolone was also found to be effective in reducing mortality in a metanalysis by Y Siegman-lgra., *et al* [8]. Doxycycline however is not suitable for children under 8 years, and alternative agents must be used.

Our patient received at least 5 years of treatment for chronic Q fever endocarditis. Despite this, the patient still has relapse. So, the question remains how long we should treat a patient post relapse?

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