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CASE REPORT

A case of non-toxigenic *Corynebacterium diphtheriae* infective endocarditis in a nine-year old child

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Abstract

Invasive non-toxigenic Corynebacterium diphtheriae infections are uncommon but increasingly being recognised as causing significant morbidity and mortality. They are non-vaccine preventable and may occur sporadically or within the context of outbreaks. Clinicians need to be aware of their potentially devastating consequences. There are limited reports from sub-Saharan Africa. We, therefore, describe a paediatric case of non-toxigenic C. diphtheriae infective endocarditis highlighting aspects relevant to infectious disease management.

Introduction

Corynebacterium diphtheriae is historically known for causing toxigenic diphtheria, a major public health threat in the pre-vaccine era.[1] The successful uptake of the diphtheria toxoid vaccine in routine primary immunisation precipitously reduced the global incidence, though intermittent outbreaks have occurred especially during disruptions of healthcare systems or vaccination programmes.[1] With this decline, the pathogenicity of non-toxigenic *C. diphtheriae* (NTCD) isolates is increasingly being recognised, and invasive disease has been associated with significant morbidity and mortality.[1-2]
Invasive NTCD disease presents as bacteraemia with metastatic sequelae including infective endocarditis, septic arthritis, osteomyelitis, and mycotic aneurysms, with a clinical course that may be fulminant or fatal.[2-3] NTCD infective endocarditis (NTCD IE) is uncommon. We describe a patient with NTCD IE who presented to a tertiary Children's Hospital in Cape Town, South Africa.

Case report

A 9-year-old girl presented in July 2021 with a 5-day history of fever. She had underlying unrepaired congenital cyanotic heart disease, characterised by complete atrio-ventricular septal defect, pulmonary valve stenosis and a double-chambered right ventricle. On examination, she was acutely ill, febrile (temperature, 39°C), tachycardic, clubbed and cyanotic but not in shock or cardiac failure. Her total white cell count was 23.6 x 10^9/L with neutrophilia and the C-reactive protein (CRP) was 59 mg/L. She tested negative for Human Immunodeficiency Virus 1/2 and Severe Acute Respiratory Syndrome Coronavirus 2. She was unwell but haemodynamically stable and commenced empirically on intravenous ceftriaxone while awaiting blood culture results and cardiac imaging.

Two positive blood cultures collected early during admission, revealed small Gram-positive bacilli on light microscopy similar to that shown in Figure 1. Grey, catalase-positive colonies were cultured on blood agar media, and black colonies were cultured on tellurite-containing agar media (both incubated aerobically at ~37°C). These microbiological features were suggestive of potential *Corynebacterium diphtheriae* infection, and organism identification was confirmed using the VITEK 2 automated system (bioMérieux, Marcy-l'Étoile, France). Minimum inhibitory concentration (MIC) to determine antibiotic susceptibility was performed using the E-TEST (bioMérieux, France) gradient diffusion method. The isolate was intermediately resistant to penicillin (MIC=0.25 ug/mL), but susceptible to ceftriaxone (MIC=1 ug/ml), and vancomycin (MIC=0.5 ug/mL) using the Clinical Laboratory and Standards Institute M45 guideline. The absence of the *tox* gene was confirmed using a real-time polymerase chain reaction assay (RT-PCR) at the National Institute for Communicable Diseases (NICD), Johannesburg, South Africa.

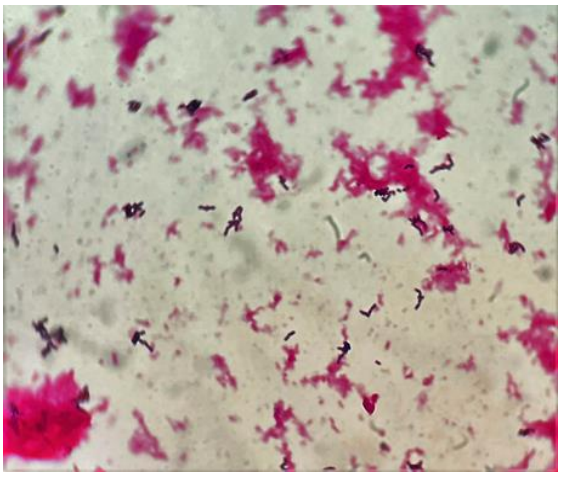

Figure 1. Small Gram-positive bacilli (purple) visualised using Gram stain and light microscopy (Courtesy of Dr Gert Marais)

A transthoracic echocardiogram (TTE) on day 2 of hospitalisation initially showed the absence of cardiac vegetations. However, on repeat TTE on day 12 of hospitalisation, a vegetation measuring 8 mm x 6.5 mm was visualised on the pulmonary valve (Figure 2). Intravenous gentamicin (for synergism) was added to the ceftriaxone in response to the confirmed vegetation. Repeat TTE on day 19 demonstrated persistence of the vegetation which had increased in size to 10 mm x 8 mm, but still without any pulmonary valve regurgitation. She continued to experience elevated temperature measurements.

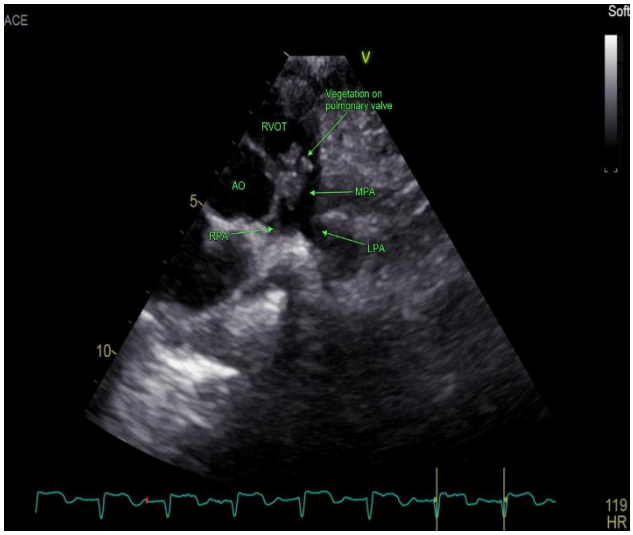

Figure 2. An Echocardiogram showing the vegetation 8 x 6.5 mm (arrow) in the parasternal short axis view (AO aorta, MPA main pulmonary artery, LPA left pulmonary artery, RVOT Right ventricular outflow tract)

Consequently, the vegetation was excised on day 26 of hospitalisation via an open-heart surgical procedure. The pulmonary valve was not significantly damaged by the vegetation. During the same surgical procedure, the underlying cardiac defects were repaired. Histopathological analysis of the excised vegetation confirmed bacterial endocarditis by demonstrating Gram-positive bacilli. Defervescence and a downward CRP trend were observed post-operatively. She completed a total antibiotic duration of 6 weeks. Screening did not reveal any evidence of nasal or oropharyngeal carriage of *C. diphtheriae* from our patient or her close contacts.

This case was one of a cluster of seven cases of suspected or culture confirmed NTCD infective endocarditis, diagnosed in the Western Cape Province of South Africa between 18 May 2021 and 2 July 2021. Their ages ranged from 9 years to 38 years. These seven patients resided in two districts in the province. Five out of these seven cases died. No clear epidemiological links between these cases were established.[4]

Discussion

There is a growing recognition of NTCD as a cause of invasive disease such as IE. The published literature, however, is limited to case reports and series primarily from well-resourced settings. In one developed setting, 11.8% of 85 episodes of paediatric IE over a period of 18 years were due to NTCD.[5] In New Zealand, a case series identified 10 *C. diphtheriae* IE cases with 80% being non-toxigenic over a 14-year period among adults and children.[6] Similarly, another case series among young adults described 4 patients with NTCD IE over a 10-year period in Australia[2]. Among African countries, a meta-analysis of IE determined culture-positivity to be 48.6% with only 18 out of 42 countries providing microbiological data and none reporting *C. diphtheriae*.[7] In our hospital, out of 49 cases of paediatric IE identified over a 5-year period, 89% were culture-positive.[8] *Corynebacterium* species was identified in one of these culture-positive cases[8]. Under-reporting from sub-Saharan Africa may reflect the lack

of laboratory capacity to identify and/or ascertain toxigenicity of *C. diphtheriae* in cultured isolates. Additionally, limited resources to perform investigations, frequent use of antibiotics before blood collection, and inadequate blood sampling procedures may contribute to low blood culture yields.[7]

NTCD are strains which do not produce exotoxin because they lack the *tox* gene acquired from lysogenic corynebacteriophages, therefore, diseases caused by these strains are not prevented by the diphtheria toxoid vaccine as disease is not toxin mediated.[1,3] Likewise, there are non-toxigenic strains which possess an inactive *tox* gene. These *tox*-bearing non-toxigenic strains (NTTB) may attain toxigenicity through lysogenic acquisition of new functional genes underscoring its public health significance.[1] Humans are natural hosts for *C. diphtheriae* and healthy individuals have demonstrated throat carriage of NTCD.[3] Although cutaneous lesions are more frequently culpable as potential sources, throat carriage of NTCD may be the source of infection.[3] In NTCD IE, detection of *C. diphtheriae* is normally via isolation from blood, excised heart valve or vegetation tissue cultures, or alternatively, *C. diphtheriae* DNA detection using molecular methods like PCR from excised valve tissue.

Risk factors for NTCD IE include congenital or acquired heart diseases, prosthetic valves, alcoholism, diabetes mellitus and intravenous drug use.[2,6] In our patient, the only identifiable risk factor was the underlying congenital heart anomaly, and no embolic phenomena or destroyed valves were noted. A recent case report from Brazil highlighted the aggressive embolic propensity of NTCD in a 21-year-old cocaine user with IE who had damaged heart valves and valvular dysfunction, complicated by an extensive splenic abscess and limb gangrene.[9] Destroyed heart valves have previously been described in NTCD IE.[2]

Although the mechanisms of pathogenicity of non-toxigenic strains are not fully understood, *C. diphtheriae* organisms rely on pili and adhesins for adherence to host cells. They also form biofilms potentially compromising antibiotic therapy.[1,3] This may have occurred in our patient where the organisms demonstrated in the excised tissue were probably protected by biofilms and could explain the sustained fever and progressive enlargement of the vegetation despite prolonged appropriate antibiotic therapy. This underscores the fact that IE is often a surgical disease requiring surgical excision of vegetations in addition to targeted antibiotics to achieve source control as well as concomitant repair of any underlying congenital or valvular heart defect. In our hospital, more than half of the children diagnosed with infective endocarditis required surgery with a trend towards lower mortality in the surgical group compared with medical therapy alone.[8]

Antimicrobial treatment of NTCD IE is not well defined and lacks the level of evidence available for IE caused by staphylococci and streptococci. A review of *C. diphtheriae* IE treatment showed no significant difference in outcome when penicillin-susceptible strains were treated with either a beta-lactam alone or in combination with an aminoglycoside (for synergism), and treatment duration mostly ranged from 4 to 8 weeks.[6] Surgical intervention for valvular dysfunction was required in 30% to 50% of NTCD IE in the above-mentioned case series with 100% survival in all patients irrespective of surgery.[2,6] In contrast, higher mortality rates ranging from 38% to 43% were noted in two reviews of reported toxigenic and non-toxigenic *C. diphtheriae* IE cohorts dating from the pre-vaccine era to the mid-2000s.[2,6] The differences in outcomes between now and then likely reflect increased expertise in cardiac imaging and management in well-resourced settings in the modern era.[6] Case fatality rates may, however, still be high in low- and middle-income countries (LMIC) as reflected in the provincial cluster, where five out of seven patients died. This may be partly due to lower levels of access to cardiac surgery in LMICs as mortality is known to be lower with early surgical management compared to medical therapy alone.[10]

In South Africa, invasive *C. diphtheriae* is a statutory notifiable disease and macrolides are offered to contacts who demonstrate carriage.[11] This may eliminate the potential for phage conversion and dissemination.[1] There is no role for anti-toxin in patients with invasive NTCD infection, but toxoid vaccination is offered to partially vaccinated or unvaccinated cases and contacts to prevent future toxigenic disease.

Conclusion

This report described invasive NTCD infective endocarditis in a child from sub-Saharan Africa. In our patient, a surgical intervention was needed for a favourable outcome despite almost four weeks of prior antibiotic therapy. NTCD IE can potentially be destructive, therefore clinicians need to be aware of its sequelae in bacteraemic patients. Clinical suspicion and early recognition of NTCD IE remains crucial and children should ideally be managed in centres where cardiac surgery is readily available.

Author contributions: YB wrote the first draft of the manuscript, HDT interpreted the microbiological results and provided figure 1. GC contributed figure 2 and assisted with the description and interpretation of the cardiac findings. BE assisted with the development of the first draft. All authors reviewed and edited the manuscript. All authors approved the final manuscript.

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Competing interests: The authors declare no competing interests.

References

1. Sharma NC, Efstratiou A, Mokrousov I, Mutreja A, Das B, Ramamurthy T. Diphtheria. Nat Rev Dis Primers. 2019 Dec 5;5(1):81.
2. Mishra B, Dignan RJ, Hughes CF, Hendel N. Corynebacterium diphtheriae endocarditis--surgery for some but not all! Asian Cardiovasc Thorac Ann. 2005 Jun;13(2):119-26.
3. Saleeb PG, Corynebacterium diphtheriae (Diphtheria) in: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th Edition. Philadelphia: Elsevier; 2019 p.2526-2531.
4. Western Cape Province Health circular H91/2021: Diphtheria alert: non-toxigenic diphtheria cluster identified in the West Coast and Cape Winelands districts; Western Cape Department of Health, South Africa; 2021
   Available from: https://www.westerncape.gov.za/assets/departments/health
5. Webb R, Voss L, Roberts S, Hornung T, Rumball E, Lennon D. Infective endocarditis in New Zealand children 1994-2012. Pediatr Infect Dis J. 2014 May;33(5):437-42.
6. Muttaiyah S, Best EJ, Freeman JT, Taylor SL, Morris AJ, Roberts SA. Corynebacterium diphtheriae endocarditis: a case series and review of the treatment approach. Int J Infect Dis. 2011 Sep;15(9):e584-8.
7. Noubiap JJ, Nkeck JR, Kwondom BS, Nyaga UF. Epidemiology of infective endocarditis in Africa: a systematic review and meta-analysis. Lancet Glob Health. 2022 Jan;10(1):e77-e86.
8. Willoughby ML, Basera W, Perkins SR, Comitis GAM, Fourie B, Lawrenson JB et al. Infective endocarditis in infants and children in the Western Cape, South Africa: a retrospective analysis. Cardiol Young. 2019 Oct;29(10):1282-1286.
9. de Santis A, Siciliano RF, Sampaio RO, Akamine M, Veronese ET, de Almeida Magalhaes FM et al. Non-toxigenic Corynebacterium diphtheriae infective endocarditis with embolic events: a case report. BMC Infect Dis. 2020 Dec 1;20(1):907.
10. Duk-Hyun Kang et al. Early Surgery versus Conventional Treatment for Infective Endocarditis. N Engl J Med. 2012;366:2466-73.
11. National Institute of Communicable Diseases (NICD). Diphtheria: NICD Recommendations for Diagnosis, Management and Public Health Response, South Africa. May 2018.

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