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***Arcanobacterium haemolyticum* CNS abscess and bacteremia following head trauma: a case report and literature review**

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Abstract

Arcanobacterium haemolyticum is an uncommon cause of pharyngitis with rash that occurs predominantly among adolescents and that has been only rarely implicated in severe or systemic infections. We report a case of subdural empyema and bacteremia due to *A. haemolyticum* in an adolescent woman following physical assault with trauma to the head, which required neurosurgical intervention combined with prolonged antibiotic therapy. We additionally describe the previous occurrences of *A. haemolyticum* culture positivity recorded over a fifteen-year period by the microbiology laboratories of the two large academic medical centers at which this patient received care, and review the epidemiology, laboratory identification, and treatment of this unusual pathogen.

Introduction:

Arcanobacterium haemolyticum (*A. haemolyticum*), is an infrequent cause of acute pharyngitis in adolescents and a rare cause of invasive infections. Laboratory identification of the organism is difficult, as it may be misidentified by biochemical testing. Though usually susceptible to penicillins in vitro, several reports of treatment failure caution against their empiric use. We report the case of an 16-year woman who presented with *A. haemolyticum* intracranial abscesses and bacteremia after a recent episode of sinusitis and head trauma following physical assault. We describe our laboratory's experience with *A. haemolyticum* isolation over the past 15 years and review the literature surrounding this unusual pathogen.

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The authors have no conflicts of interest to disclose.

Case Presentation:

A 16-year-old girl presented to the emergency department with nausea, vomiting and altered mentation 48 hours after a physical assault. She reported head trauma with loss of consciousness during the assault. She also reported 5 days of cough, congestion, and sore throat. On exam, her temperature was 37.7°C with a heart rate of 122 beats/minute. She was somnolent and disoriented with nuchal rigidity, a positive Brudzinski's sign, and skin abrasions above her left eyebrow. Laboratory evaluation revealed a white blood cell count of 29,000 cells/ μ l. Head Computerized Tomography (CT) showed pneumocephalus near the left lateral aspect of the crista galli and a small left frontal scalp hematoma, suggesting occult fracture.

The patient was given meningitic doses of ceftriaxone and vancomycin and admitted to the hospital. Ampicillin-sulbactam was added the next day. She became more lucid but developed worsening headache. Repeat CT of the head showed interval development of contusion, punctate hemorrhages in the bilateral gyrus recti and inferior frontal gyri, and mass effect from evolving edema in the left inferior frontal gyrus. Lumbar puncture was deferred in light of these findings.

Blood cultures drawn on admission grew gram variable rods from aerobic and anaerobic bottles, which were subcultured onto 5% sheep's blood agar as well as MacConkey, chocolate, and Brucella agar plates as per standard laboratory protocol for blood culture specimens. Biochemical identification using the RapidID™ CB Plus kit (Thermo Scientific) identified the organism as *Arcanobacterium pyogenes*. Vancomycin and ceftriaxone were stopped and ampicillin/sulbactam was continued. A transthoracic echocardiogram showed no vegetations. She was transferred to Texas Children's Hospital for continuing care.

The patient developed tonic-clonic seizures and became increasingly confused. Magnetic Resonance Imaging (MRI) showed anterior and inferior left frontal lobe cerebritis with early abscess formation, regional mass effect and meningitis. She was taken to the operating room for bifrontal craniotomy with exenteration of the frontal sinuses and evacuation and washout of a subdural empyema. Surgical cultures resulted in no growth, but universal PCR using 16S rRNA primers sent from the sinus tissues identified *A. haemolyticum*, *Bacteroides* sp., *Anaerococcus tetradius*, *Dialister micraerophilus*, *Erysipelotrichaceae* sp., and *Propionibacterium acnes*. Confirmatory 16S rRNA sequencing of the initial blood cultures identified the isolate as *A. haemolyticum*.

Following surgery the patient's mental status returned to baseline. Vancomycin, ceftriaxone, and metronidazole were selected as definitive therapy and the patient received four weeks of treatment, after which repeat MRI showed post-surgical changes without infection. She was discharged home with an additional 2 weeks of amoxicillin/clavulanate.

Discussion:

A. haemolyticum is a gram-positive, catalase-negative, nonmotile and non spore-forming bacillus previously assigned to the genera *Corynebacterium* and *Actinomycetes* [1]. It may

be easily mistaken for *A. pyogenes*, a veterinary pathogen of economic importance as a common cause of mastitis in livestock, using rapid biochemical identification methods.

A. haemolyticum is primarily a human pathogen, though animal infection has been described [2]. In clinical practice it is best known as a cause of acute pharyngitis with exanthem in adolescents and young adults. The rash occurs in about half of all cases of *A. haemolyticum* pharyngitis, and is typically an erythematous scarlatiniform, urticarial or morbilliform rash involving the trunk and extremities and sparing the face, palms and soles [3]. In a two-year review of throat swabs taken from patients in 3 hospitals in Ottawa, Canada, *A. haemolyticum* was recovered from 42 of 11,159 patients and none of 2,241 healthy controls. The prevalence was highest in adolescents aged 15–18 years, in whom *A. haemolyticum* represented 2.5% of recovered clinical isolates [4].

In another review of pharyngeal cultures, over 90% of the recovered *A. haemolyticum* isolates came from patients between the ages of 10 and 30 years [5]. However, the true prevalence of this organism in acute pharyngitis is probably underestimated because it grows more readily on human blood agar than the routinely used sheep blood media, and because clinical laboratories may misidentify *A. haemolyticum* as streptococci on the basis of its colony morphology, beta-hemolysis, and cross-reactivity with streptococcal antisera [4,6].

Beyond pharyngitis, *A. haemolyticum* has been primarily associated with other infections of the head and neck, such as Lemierre's syndrome, tonsillar abscess, thyroid abscess, and brain abscess following dental instrumentation [7–10]. In addition, several cases of wound infections and osteomyelitis with this organism have been reported. In most of these cases *A. haemolyticum* appears to be one constituent of a polymicrobial infection, though in one report of a patient with osteomyelitis and sepsis *A. haemolyticum* was recovered in pure culture [6,11–12]. *A. haemolyticum* may rarely cause other invasive infections in immunocompetent hosts, including bacteremia, infective endocarditis, and pyothorax [13–15]. Involvement of the central nervous system appears to be common in patients with bacteremia or other invasive infections with this organism, occurring in 6 of 23 patients described in one case series [16].

Investigating for other cases of *A. haemolyticum* bacteremia in our community, we reviewed culture data obtained between January 2000 and April 2015 from the clinical laboratories of the two teaching hospitals to which our patient was admitted, Texas Children's Hospital (TCH) and Ben Taub General Hospital (BTGH). These labs report data from their primary institutions as well as satellite clinics. *A. haemolyticum* was isolated from 26 cultures (9 from the TCH system, 17 from BTGH) taken from 21 patients during the study period. Of these 26 cultures, 15 were oropharyngeal, 7 were wound, abscess or tissue cultures from the breast, perirectum or extremities, one was urinary, one was peritoneal fluid, and two were blood cultures, both from our patient; the BTGH microbiology laboratory processed an estimated 288,000 blood culture specimens during this period, while the TCH laboratory processed an estimated 460,000 blood and 46,000 throat swab culture specimens. All nine of the TCH cultures were oropharyngeal, collected from patients aged 7–17, and 5/9 were aged 14–17.

Antibiotic therapy for serious *A. haemolyticum* infections should be tailored to the antibiotic susceptibilities of the individual isolate in question. This organism is almost universally resistant to trimethoprim-sulfamethoxazole. With the exception of 1 report of high level resistance, most strains remain sensitive to clindamycin and macrolides [17]. Minimum Inhibitory Concentrations (MIC) to vancomycin, doxycycline, and ciprofloxacin are generally low, but these agents have not been often used in the reported literature [18]. Penicillins have been the most frequently prescribed agents historically, in some cases with good clinical success, and *A. haemolyticum* appears to be susceptible to a broad range of beta-lactams by traditional MIC cutoffs. However, *A. haemolyticum* has shown tolerance to penicillins *in vitro* and has been associated with clinical failure necessitating change of therapy in some acute pharyngitis cases [19–20]. In Banck and Nyman's investigation of *A. haemolyticum* pharyngitis, penicillin failed to achieve microbiologic cure by serial throat culture at eight weeks in 80% of cases, even when prescribed at high doses; by comparison, eradication of the organism was achieved in 87% of patients prescribed erythromycin [19]. Penicillins may therefore not be ideal as initial monotherapy in serious infections involving *A. haemolyticum*. Previous authors on this topic have suggested the empiric combination of high-dose penicillin and erythromycin.

A. haemolyticum is an uncommon human pathogen most frequently associated with acute pharyngitis, often with a rash, in the adolescent and young adult population. It is rarely associated with invasive and systemic infections. To the best of our knowledge this is the first case of sinusitis and subsequent craniofacial trauma leading to *A. haemolyticum* central nervous system infection in an otherwise immunocompetent patient. Although most isolates appear sensitive to the penicillins by laboratory testing, concerns about *in vivo* efficacy and reports of clinical failures suggest empiric multidrug therapy may be indicated for patients presenting with serious *A. haemolyticum* infections. This case serves as a reminder that head trauma can result in serious central nervous system infections due to upper respiratory flora. *Arcanobacterium haemolyticum* remains a diagnostic challenge requiring a high index of suspicion in patients with preceding upper respiratory symptoms as well as an awareness of the limitations of routine laboratory testing for identification of this organism.

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