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Recurrent stridor in a 9-year-old boy

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Abstract

Case Report: An otherwise healthy 9-year-old, fully vaccinated, male initially presented with acute onset of sore throat, fever, trouble swallowing, and mild intermittent dyspnea. Due to worsening respiratory distress, the patient was brought to the emergency department where he was found to have hoarse voice, stridor, and trismus. Concerned for upper airway obstruction, the medical team obtained a lateral neck X-ray, which confirmed our suspicion for epiglottitis. Patient's blood cultures grew *Haemophilus influenzae* at 48 hours. Further history revealed that our patient was diagnosed with Group B *Streptococcus* (GBS) meningitis at 6 days of age, two episodes of acute otitis media and an episode of epiglottitis 3 years prior. Due to bacteremia, recurrent epiglottitis and history of GBS meningitis, an immunodeficiency evaluation was initiated. Initial labs showed normal immunoglobulin levels and normal levels of complement factor C3 and C4. However, the patient had abnormal CH50 activity, < 10 and < 13 on repeat (normal: 31 - 60 U/mL). Further immunological studies revealed undetectable C2 factor level which confirms complement factor C2 deficiency.

Discussion: A thorough history-taking is crucial in the diagnosis of this patient's underlying immunodeficiency given the patient had been growing and developing normally and was perceived to be relatively healthy. Prevalence of primary immunodeficiencies in children is about 1 in 2,000. Initial immunological work up with normal immunoglobulin levels made humoral deficiency less likely in this patient. His C3 and C4 levels were normal, but his complement activity, measured by CH50, was significantly low, indicating a problem within his complement cascade. Complement deficiencies are rare and make up less than 10% of primary immunodeficiencies. Of those, complement factor C2 is the most frequently affected factor.

Conclusion: History of recurrent serious bacterial infections in a child should prompt pediatricians to consider immune system dysfunction. Not all immunodeficiencies present early in childhood with frequent invasive infections. Having recurrent epiglottis is especially rare, a unique component of our patient's history that ultimately led the medical team to evaluate for immune deficiency.

Keywords

CH50 immunodeficiency; encapsulated organisms; epiglottitis; supraglottitis.

Introduction

Children with epiglottitis usually present with fever, sore throat, difficulty swallowing, and difficulty with neck flexion. They may not necessarily seem ill at first, but respiratory distress can rapidly develop with presence of stridor and tripoding posture. Thus, timely diagnosis with physical exam and imaging (lateral neck x-ray) is essential. Other differential diagnoses for a child presenting with an isolated or recurrent episodes of stridor should include foreign body aspiration, laryngeal/tracheal mass, vocal cord paralysis, acute tonsillitis, and peritonsillar or parapharyngeal abscess. In this case report of a 9-year-old boy, prompt diagnosis of epiglottitis was based on his classic physical exam and imaging (chest and lateral neck x-ray), making other differential diagnoses unlikely in the process. *Haemophilus influenzae* is the most common cause of epiglottitis. Incidence of infection has decreased dramatically due to the *Haemophilus influenzae* type B (Hib) vaccine in the past 30 years. The vaccine is 90-95% effective, but it does not contain all strains of *Haemophilus*. Epiglottitis therefore can still occur despite vaccination [1,2]. While it was not unusual for our patient to be diagnosed with epiglottitis at this age, additional history demonstrated that he had 1 prior hospital admission for stridor and respiratory distress consistent with epiglottitis. It was this particular history component that was highly unusual, leading the medical team to pursue additional evaluation.

Case Presentation

A 9-year-old, fully vaccinated male, presented to urgent care with acute onset of sore throat, fever, trouble swallowing, shotty cervical lymphadenopathy and mild intermittent dyspnea. Rapid strep screen performed was negative and patient was sent home with recommendations for supportive care. Due to worsening respiratory distress, the patient was brought to an outside Emergency Department where he presented in sniffing position along with a hoarse voice, stridor, and trismus. Laboratory evaluation was significant for leukocytosis (WBC 17.3 Th/uL) with a left shift (ANC 16,089 uL) and elevated C-reactive protein (CRP 21.60 mg/dL). Lateral X-ray of the neck demonstrated thickening of the epiglottis and aryepiglottic folds (Image 1). He received methylprednisolone, ceftriaxone, and vancomycin for presumed epiglottitis and was admitted to the pediatric intensive care unit (PICU).

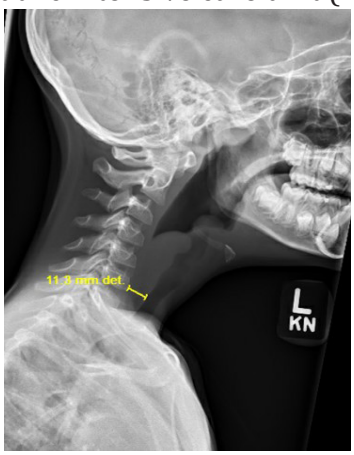

Figure 1: Lateral X-ray demonstrating thickening of the epiglottis and aryepiglottic folds.

Additional history revealed a normal pregnancy ending in an uncomplicated delivery at 39 weeks of gestation. At 6 days of age, the patient was admitted to the hospital with Group B *Streptococcus* meningitis requiring intravenous antibiotics. Since then, the patient has been growing appropriately along the 10-20th percentile for weight and 50th percentile for height. Three years prior to his current presentation, at 6 years of age, our patient was hospitalized in the PICU for respiratory distress in the setting of a sore throat, hoarse voice, fever, and stridor. Neck X-ray demonstrated "steeple" and "thumb" sign. Bedside laryngoscopy showed diffuse supraglottic edema involving the bilateral arytenoids and epiglottis without exudates (Image 2A & 2B). Patient was treated with racemic epinephrine, oral steroid, ceftriaxone, vancomycin, and Heliox. Blood culture was negative at the time. Repeat laryngoscopy after hospital discharge showed resolution of edema and normal anatomical structures (Image 2C & 2D).

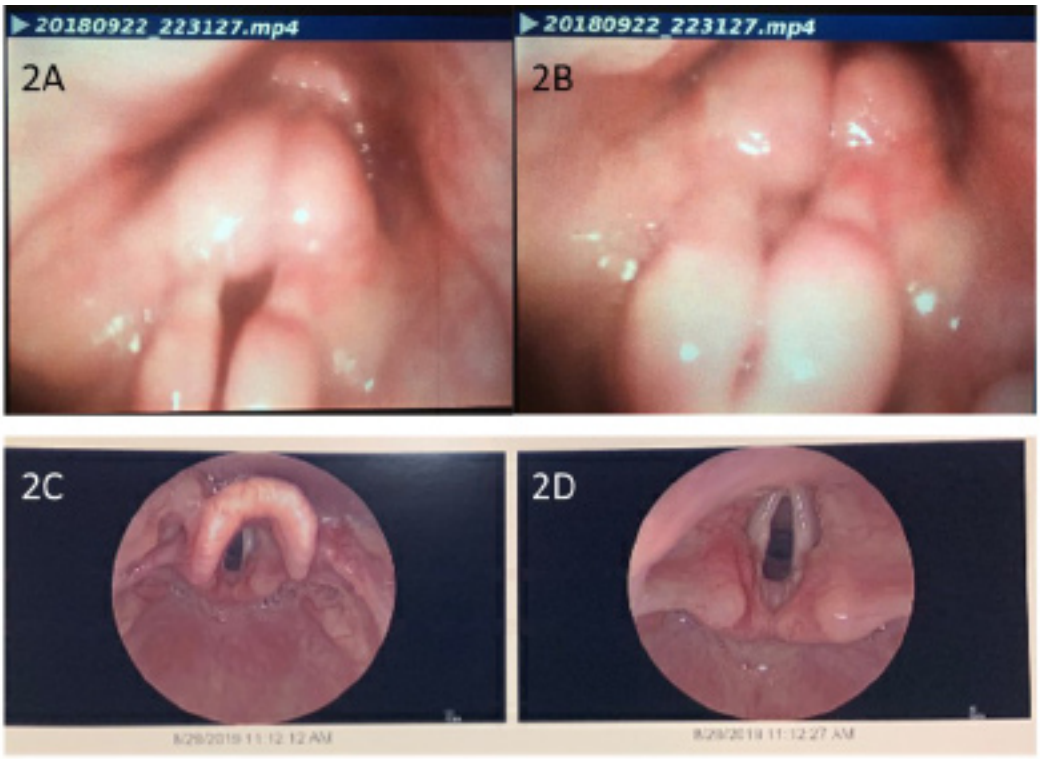

Figure 2: Bedside flexible laryngoscopy performed by Otolaryngology on admission showed diffuse supraglottic edema with inability to visualize vocal cords (2A & 2B). Laryngoscopy was repeated about one year after hospital admission with normal anatomy (2C & 2D).

Parents recalled two episodes of acute otitis media but no other infections such as sinusitis, pneumonia, cellulitis or abscess. There was no family history of recurrent infections, autoimmune disease, recurrent unexplained angioedema or immunodeficiency. Patient's three siblings were healthy and fully immunized.

While in the PICU during this current admission, otolaryngology again performed bedside flexible laryngoscopy, which showed findings consistent with epiglottitis. Respiratory pathogen panel and strep culture were negative. At 48 hours, patient's blood culture grew *Haemophilus influenza.*

Due to *Haemophilus influenzae* bacteremia, recurrent epiglottitis, and history of GBS meningitis, an immunological work up was initiated. Immunoglobulins (A, G, M) were within normal range. Complement C3, C4, and C1 inhibitor proteins were within normal range, but his CH50 activity was <10 (normal: 31 - 60 U/mL) and < 13 on repeat. Titer for *Haemophilus influenzae* type B (Hib) Ab IgG was indeterminate.

Streptococcus Pneumoniae IgG Ab (13 Serotypes) titers demonstrated adequate levels in only 2 out of the 13 strains. Tetanus antitoxoid antibody was normal. Peripheral smear was negative for Howell-Jolly bodies and abdominal ultrasound demonstrated normal size spleen. Besides some shotty cervical lymphadenopathy, patient was not noted to have enlarged axillary, supraclavicular or inguinal lymph nodes. Complement factor 6, 7, and 9 were normal, but factor 2, 5, and 8 were low (Table 1). After completion of work up, our patient was diagnosed with recurrent epiglottitis secondary to complement factor 2, 5, and 8 deficiency.

Table 1: Laboratory studies of immunoglobulins, total complement activity and individual complement factors.

Lab	Reference Values	During Hospitalization	2 Months After Discharge	4 Months After Discharge
Total lgG*	mg/dL	704 (582-1441)	819 (673-1734)	
lgA*	mg/dL	137 (58-204)	164 (41-368)	
lgM*	mg/dL	62 (21-140)	105 (47-311)	
C4 Complement	14-44 mg/dL	31	26	
C3 Complement	80-170 mg/dL		120	
Complement Total		<10	<13	
(CH50) Activity C1 Inhibitor Protein	21-39 mg/dL	26		
C2 Complement	1.6-3.5 mg/dL			<1.3
C5 Function	13,700-37,900 units/mL			9,158
C6 Function	14,363-38,940 units/mL			15,929
C7 Function	12,337-33,836 units/mL			33,796
C8 Function	18,532-53,364 units/mL			18,037
C9 Function	8,310-42,320 units/mL			19,926

Hospital/Outpatient Course

After diagnosis of epiglottitis was made, patient was started on ceftriaxone, vancomycin, racemic epinephrine, and intravenous methylprednisolone. Patient responded well to therapy with improvement in overall respiratory status. He was discharged on 10 days of intramuscular ceftriaxone to complete treatment for *H. influenzae* bacteremia. He was followed by Immunology after hospital discharge in order to complete his immunodeficiency evaluation. Additionally, his *Haemophilus* conjugate vaccine series was repeated after going home. He also received Pneumococcal Polysaccharide Vaccine-23 Valent and Meningococcal Conjugate vaccine early. Repeat Pneumococcal and Hib titers demonstrated adequate post-vaccination response.

Discussion

A thorough history taking is crucial in the diagnosis of this patient's underlying immunodeficiency. As seen in our patient's case, children with classical pathway complement deficiency, such as C1, C2 and C4, are at risk of developing infections with encapsulated bacteria like *S. pneumoniae*, *H. influenzae* and *N. meningitidis* [3,4]. A retrospective analysis in 2015, looking at children with recurrent invasive pneumococcal

disease, found that 6 of 15 children who were tested for immunodeficiencies were C2 deficient [5]. Thus, an underlying immunodeficiency can be easily missed in a normally growing 9-year-old boy with epiglottitis if additional history did not reveal a prior episode of epiglottitis. Once our patient's recurrent serious bacterial illnesses were uncovered, the medical team had high concern for an underlying immunodeficiency.

Prevalence of primary immunodeficiencies in children is about 1 in 2,000 [6]. As there was no structural airway abnormality, congenital finding, skin manifestation or developmental delay, our patient's problem was most likely due to the immune system. With normal immunoglobulin levels and adequate post-vaccination titers, humoral deficiency was thus less likely. Abnormal CH50 and low C2 complement level, on the other hand, suggested complement deficiency.

Complement deficiencies are rare, making up less than 10% of primary immunodeficiencies with the most frequently affected factor being C2 [7]. The complement arm of the innate immune system is responsible for opsonization and inflammatory response activation [8]. Complement activity can be measured through CH50 level, which evaluates the nine complement components that allow for lysis (C1-C9) [9]. Our patient's CH50 level was low, indicating a problem with this portion of the complement pathway. His low C2 level was consistent with our pattern of findings and thus our ultimate diagnosis.

The basis of complement testing is based on evaluating individual protein levels and overall activity of the cascade. The CH50 assay measures classical pathway activity while another, AH50, measures alternative pathway [10]. Although CH50 is a fast way to assess complement activity, the test is not very sensitive for evaluating small changes in the complement spectrum. Specimen handling has also been shown to affect the level of complement activity [9]. Therefore, it is always recommended to repeat CH50 to confirm abnormal values. In our patient's case, CH50 activity was low on two separate occasions measured two months apart, confirming our suspicion for immunodeficiency.

Deficiencies in the classical pathway components have been associated with increased susceptibility to Systemic Lupus Erythematosus (SLE), especially in patients with C1q deficiency [11]. C1q participates in apoptotic debris removal and a deficiency in this protein leads to impaired uptake of debris. It is hypothesized that the absence of C1q leads to impaired handling of immune complex and inadequate clearance of apoptotic cell debris. Another hypothesis suggests that apoptotic cells may represent an important source of autoantigens, breaking self-tolerance and triggering autoimmune diseases [12]. In the European Society for Immunodeficiencies registry, 37% of the 77 classical pathway complement deficiency patients have SLE-like disease [13]. The prevalence of SLE in homozygous C2 deficient patients appears to be between 10-30%. Lupus, when associated with complement deficiency, presents at an earlier age and tends to exhibit more aggressive symptoms with worse prognosis than those without an associated immunodeficiency. There were no findings to suggest autoimmune disease in our patient or his family. It was important for our patient's family to be aware of this association and stay vigilant of any joint pain or rash. All in all, immunodeficiency and autoimmunity can co-exist and are oftentimes intertwined in immunodysregulatory syndromes.

An adult retrospective study of patients with invasive bacterial infections due to encapsulated organisms showed that 9 of 38 patients were found to have primary immunodeficiencies. Seven of the 9 patients were diagnosed after their first episode, while the other two were diagnosed after the second episode of encapsulated organism infection. Three patients were found to have complement deficiencies [14]. Though its prevalence remains low, in those with recurrent infections, primary immunodeficiencies should be considered on the differential. Having recurrent epiglottis is especially rare, making it one of the components of our patient's history that pushed us into proceeding with an immunological work up.

Conclusion

Recurrent serious bacterial infections in a pediatric patient should prompt evaluation of the immune system. Not all immunodeficiencies present early in childhood with multiple invasive infections. It is unclear how many children with more than one serious or invasive bacterial infections have underlying primary immunodeficiencies. More data needs to be collected on the true prevalence of immunodeficiencies in pediatric populations, especially those who are not identifiable within the first few years of life.

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