Fait Clinique

When Whooping cough is complicated by encephalitis/Encephalopathy in infants
Quand la coqueluche est compliquée d'une encéphalite /encéphalopathie

Tilouche.S [1,2], Ghorbel.S [1,2] , Labbaoui.R [1,2], BenBelgacem.H , Tilouche.L [3], Tej.A [1,2], Ben Khadim Allah. K [1] ,Bouguila.J , Smaoui.H [4] , Boughamoura.L [1,2].

[1] University of Sousse, Faculty of Medicine of Sousse "Ibn El Jazzar",
[2] Farhat Hached University Hospital, Department of Pediatrics, Sousse, Tunisia.
[3] Sahloul University Hospital , Microbiology Laboratory, Sousse , Tunisia
[4] Children's Hospital of Tunis , Microbiology Laboratory, , Tunisia

ABSTRACT :

Pertussis is a common infection. However, encephalitis/encephalopathy is a rare and severe complication To Whooping cough. In this article, we report two Tunisian cases of encephalitis/encephalopathy complicating a pertussis .

Case 1: A 6-week-old infant was admitted for dyspnea and cough . On examination, his respiratory rate was 64 breaths/min . Her oxygen saturation was 96% on room air. The investigations showed a lymphocytosis at 34800 / dl. Pertussis was confirmed by polymerase chain reaction (PCR) on nasopharyngeal swab. He received oral erythromycin. Three week later, the child presented a poor mental response and seizures. The diagnosis of encephalitis was made after having a positive cerebrospinal fluid (CSF) PCR for Bordetella pertussis. The patient was treated by intravenous (IV) erythromycin and he made an uncomplicated recovery.

Case 2: A 3-week-old female infant admitted for dyspnea with a paroxysmal cyanogenic cough. She was apyretic, there were signs of respiratory distress. Pertussis was suspected and the patient was put on macrolides. Surveys showed a white blood cell count of 68700 / dL with lymphocytosis at 29500 / dL. On the fourth day of admission, the patient presented a deterioration of the mental state. She was admitted to the pediatric intensive care unit (PICU), intubated and ventilated. The diagnosis of encephalitis was made through a positive PCR on nasopharyngeal aspiration and on CSF. The patient was treated with erythromycin IV, but the outcome was fatal.

Conclusion: These cases draw attention to severe encephalitis secondary to pertussis, pathology preventable by vaccination.

RESUME :

La coqueluche est une infection fréquente. Cependant, l'encéphalite est une complication rare et grave de la Bordetella pertussis. Dans cet article, nous rapportons deux cas tunisiens d'encéphalite compliquant une coqueluche .

Cas 1 : Un nourrisson agé de 6 semaines a été admis pour dyspnée et toux. À l'examen, sa fréquence respiratoire était à 64 cycles/min. Sa saturation en oxygène était à 96% à l'air ambiant. Les investigations ont montré une lymphocytose à34800 / dl. La coqueluche a été confirmée par PCR sur écouvillonnage nasopharyngé. Il a reçu de l'érythromycine par voie orale .Trois semaines plus tard, l'enfant avait présenté une altération de l'état de conscience et des convulsions. La PCR pour Bordetella pertussis est revenue positive au niveau du LCR. Le diagnostic d'encéphalite a été retenu. Le patient a été traité par érythromycine IV et l'évolution était favorable sans complication.

Corresponding Author
Samia Tilouche ; Institutional affiliation: University of Sousse, Faculty of Medicine of Sousse "Ibn El Jazzar", Farhat Hached University Hospital, Department of Pediatrics, Sousse, Tunisia
Email: samiatilouche@yahoo.fr
Telephone number: 00216 25 33 48 58

Cas 2 : Une petite fille âgée de 3 semaines admise pour dyspnée et toux cyanogène paroxystique. Elle était apyrétique, et elle avait une dyspnée. La coqueluche a été suspectée et le patient a été mis sous macrolides. La numération de la formule sanguine avait montré un nombre de globules blancs de 68700 / dL avec lymphocytose à 29500 / dL. Le quatrième jour de l'admission, la patiente a présenté une aggravation de l'état de conscience .Elle a été admise aux soins intensifs, intubée et ventilée. Le diagnostic d'encéphalite a été posé et des PCR sur l'aspiration nasopharyngée et sur le LCR sont revenus positives . Le patient a été traité avec de l'érythromycine IV, mais l'issue était fatal.

Conclusion: Ces cas attirent l'attention sur cette complication particulière qui est l'encéphalite secondaire à la coqueluche, pathologie évitable par la vaccination.

Keywords: Pertussis, Whoopingcough ,Encephalitis, infant, case reports

Mots clés : Coqueluche, encephalitis ,nourrisson, rapports de cas

ABBREVIATIONS:

ADEM : acute disseminated encephalomyelitis
CNS : central nervous system
CSF : CSF cerebrospinal fluid
CXR : chest x-ray
EEG : Electroencephalogram
IV : Intravenous
MRI : Magnetic Resonance Imaging
O2 : oxygen saturation
PCR : polymerase chain reaction
PICU : Pediatric intensive care unit
PT : Pertussis toxin
RT-PCR : Reverse transcription polymerase chain reaction
WBC : white cell count

INTRODUCTION :

Pertussis or whooping cough is an endemic highly infectious vaccine-preventable disease .The disease spreads through the cough and sneezing droplets which, makes it a common clinical problem in the pediatric population (1).It continues to be a public health concern for many reasons. First, during the two last decades, outbreaks have been reported in countries with high vaccination coverage. Second, pertussis remains an important cause of morbidity and mortality in infants worldwide.
Classic pertussis is a cough illness. Pertussis encephalitis is rare and the mechanism is still debated.
In this report, we describe two cases of pertussis encephalitis /encephalopathy, admitted to the department of Pediatrics in Farhat Hached hospital in an attempt to identify clinical symptoms and to highlight the necessity of performing a PCR in the Cerebrospinal fluid (CSF).

Case reports

Case1:

A 6-week-old male infant presented with dyspnea and cough that did not improve by symptomatic treatment, which began 10 days before admission. On physical examination, he was neurologically normal, his respiratory rate was 60 breaths per minute and his heart rate was 156 beats per minute. Pulse oximetry showed a hemoglobin oxygen saturation (O2) of 96% in air. Bilateral wheezes and crackles were detected . Biological examinations showed leukocytes at 70000/mm3 and lymphocytes at 34800/mm3. Markers of inflammation were normal and blood cultures were negative. The chest x-ray (CXR)showed bilateral interstitial and bronchial syndrome without obvious focus . Respiratory syncitial virus test was negative. Pertussis was suspected and confirmed by real-time PCR performed on nasopharyngeal aspirate. He received then oral clarithromycin.
Two days later, his respiratory function worsened and his heart rate increased to 180 beats per minute with normal heart sounds and pulses. Blood pressure was 80/50 mmHg. Pulse oximetry showed a hemoglobin oxygen saturation (O2) of 80%. The blood leukocyte count increased to 85,000/mm3. he was put on an O2 mask, which resulted in a rapid correction of her pulse oximetry readings to 99%.
A CXR demonstrated bronchopneumonia. An electrocardiogram demonstrated sinus tachycardia, and an echocardiogram was normal. The infant was transferred to the pediatric intensive care unit (PICU) for further management. He was started on intravenous Cefotaxime and Amiklin. Clinical Improvement was observed on the 7th day of hospitalization. However, two weeks later, the child presented with poor mental response and partial seizures lasting 10 minutes. His seizures were rapidly controlled with intravenous Diazepam. His temperature was 38.6°. A puncture was performed. Cytological analysis of her CSF showed leukocytes at 11 elements/mm3 and red blood cells at 20 elements/mm3. The biochemical study revealed a glycorachy of 3.5 g/l and a proteinorachy of 0.7 g/l with a glycorachy/glycemia ratio of 0.8. The bacterial culture of the CSF was negative. The search for the herpes simplex virus 1 genome in the CSF was negative. The PCR for Bordetella pertussis in the CSF was positive. Magnetic resonance angiography of the brain was normal. Pertussis-associated encephalitis/encephalopathy was suspected. The infant was started on intravenous immunoglobulin at a dose of 1 g/kg/day for 2 days and intravenous erythromycin at a dose of 50 mg/kg body weight /per day in three divided doses for 14 days. The cough became less frequent and the evolution was favorable. No abnormalities were detected on physical examination and the patient was discharged on day 30 after admission.

Case 2 :

A 3-week-old girl was admitted to the pediatric ward for dyspnea with paroxysmal cyanogenic cough. She was born at term by normal vaginal delivery, with no remarkable neonatal events. The girl's mother had a history of prolonged paroxysmal cough for 3 weeks. On examination, the body temperature was 37.6°. The patient had polypnea at 65 breaths per minute with intercostal draw. Pulse oximetry showed a hemoglobin oxygen saturation (O2) of 98% in air. Lung auscultation revealed bilateral wheezes and crackles. Heart rate was 140 beats per minute. Neurologic examination was normal.

Pertussis was suspected because of the infant's persistent cyanotic cough. She was there fore started on clarythromycin. Biological examinations showed a white blood cell count of 68.700/mm3 with a lymphocytosis of 29.500/mm3. The evolution was marked, five days later, by the appearance of fever. A CXR showed an opacity of the right apical lobe. A lumbar puncture was performed. Cytobacteriological and biochemical analysis of the CSF were normal. The infant was diagnosed with severe pneumonia and treated within intravenous cefotaxim and gentamycin. Four days later, the outcome was marked by worsening respiratory distress, tachycardia that reached 200 beats per minute, and drowsiness. Real-time PCRs for Bordetella pertussis genome on nasopharyngeal aspirates and CSF were positive. The patient was intubated and started on intravenous erythromycin, but her condition deteriorated rapidly and the outcome was fatal after 4 hours of ventilation.

DISCUSSION :

Pertussis is a strictly human bacterial respiratory infection, very serious for newborns (1). It remains endemic with a steady increase in the number of reported cases. Two peaks in the incidence of pertussis occur in pediatric patients: infants younger than 6 months of age who are inadequately protected by the current immunization schedule and adolescents 11 through 18 years of age (2).

The disease agents are Bordetella pertussis and parapertussis. These extracellular bacteria, which secrete toxins and adhesins, are responsible for the local and systemic cytopathic effects observed during the disease, such as destruction of the ciliated respiratory epithelium and hyperlymphocytosis(1). The presenting symptoms of pertussis in unimmunized children and infants are described as occurring in 3 phases: catarrhal, paroxysmal, and convalescent. Newborns and children who are unimmunized or partially immunized experience the most severe disease(3).

The mortality is estimated to 1% for infants under the age of 6 months (4). Complications of pertussis occur within the paroxysmal period. They are divided into 3 distinct categories: pulmonary, central nervous system (CNS), and non-CNS complications (4). Neurological complications secondary to pertussis infections, mainly seizures (febrile as well as afebrile), mental backwardness, spastic paralysis, myelitis, visual disturbances and encephalopathy have long been described. Pertussis encephalitis/encephalopathy is an uncommon but serious complication occurring in 0.5%–1% of all cases, but higher in those under 2 years old (5). Several hypotheses have been advanced to explain the physiopathology of this complications : system haemorrhage due to increased venous pressure from coughing paroxysms, hypoxia, vascular occlusions/venous stasis from lymphocytic plugs, hypoglycaemia, exacerbation of unrecognized underlying neurological conditions and effects of toxins produced by B.pertussis, Some studies showed that toxins produced by B. pertussis may create an autoimmune responses resulting in encephalitis/encephalopathy. Pertussis toxin (PT) is known of creating an autoimmune demyelinating disease in mice (6). Some other studies showed that proinflammatory cytokine production was amplified by the PT. Although the organism has never been isolated from CSF(5). For our patients, encephalopathy was a complication that occurred during malignant whooping cough. Identifying higher-risk infants earlier might allow for more rapid implementation of interventions(7). A recent retrospective analysis of records of children with critical pertussis in the PICU of a tertiary care hospital in northern India showed that there was a high prevalence of encephalopathy (>50%), compared with previous studies (8).The diagnosis should be suggested by seizures with pertussis infection, when there is no other diagnosis . He may also present with deteriorating neurological status, lethargy or coma(9). Other symptoms may appear such as paresis and plegia, ataxia, aphasia, blindness, deafness, decerebrate postures (10) and central hypoventilation(11). One of our patients presented with deterioration of neurological status and consciousness and the other presented with seizures that were rapidly controlled. An elevated and rapidly rising white cell count(WBC) count exceeded 30 000 elements/mm3; heart rates that exceeded 170 beats /min, and respiratory rates that exceeded 70 breaths/min are suggested as a predictor of severe B.pertussis infection in young infants . Making early and repeated WBC count determinations is therefore critical in the evaluation(7) . Furthermore, close monitoring of heart and respiratory rates is imperative because these were demonstrated to correlate with more severe disease progression .When necessary early consideration of exchange transfusion in the management of infants at high risk for severe pertussis(7). The diagnosis might associate abnormality within the electro-encephalogram such as signs of diffuse dysfunction(11). The Magnetic Resonance Imaging (MRI) may show abnormalities within the white cerebral matter, these lesions may look like an acute disseminated encephalomyelitis (ADEM)(12). In our case the diagnosis of encephalitis was made

with clinical presentation and the positive PCR for Bordetella pertussis in the CSF. The MRI was practiced within one of our patients and showed no radiological signs of encephalitis.
Today, PCR-based methods have largely replaced culture as the preferred diagnostic tool to identify Bordetella species from respiratory secretions in early stages of the disease(13).
Higher sensitivity and rapid report of results are the major advantages compared with conventional culture(14).However, PCR should be applied in the early and mid phase of suspected pertussis disease (up to 3 weeks), if not the strength of serology is superior in late phases and in retrospective as well as for the assessment of sero-prevalence in epidemiologic studies(15).In the case of our patients, B. pertussis was detected with the Reverse transcription polymerase chain reaction (RT-PCR) in the CSF. This examination is not frequent within the diagnosis methods. However, it's an examination that may facilitate the diagnosis of pertussis encephalitis if there is no radiological or electric signs on the electroencephalogram (EEG).
Treatment of pertussis should be both symptomatic and etiologic, directed against the causative organism with antibiotics.
It was quoted that patients suspected of having pertussis should receive antibiotic therapy before the diagnosis is confirmed (16). In the catarrhal phase, antibiotics can reduce the severity of symptoms and duration of illness, as well as accelerate the clearance of bacteria from the nasopharynx(16). In the paroxysmal phase, antibiotic therapy is indicated to reduce transmission by eliminating nasopharyngeal bacteria after 5-7 days from the start of treatment(16).
Macrolides were the first molecules to be prescribed and all studies published before 1996 recommended the use of erythromycin at a dose of 40 mg/kg/day every 6 hours for 7-14 days.
On the other hand, recent studies have demonstrated equal efficacy and better tolerability of other macrolides, such as azithromycin (16).
The choice of adjuvant therapy depends on the pathophysiological mechanism involved. The pathogenesis of encephalitis in our cases was unclear. However, an immune-mediated process was highly suspected. Proinflammatory cytokines and chemokines were associated with the development of acute encephalitis/encephalopathy (17).Measuring proinflammatory cytokine in the CSF was not possible for our patients. However an immune mediated reaction was highly suspected. Therefore, the patient who had received human immunoglobulin , had a better outcome . For our patients, encephalitis /encephalopathy was a complication that occurred during malignant whooping cough. Identifying higher-risk infants earlier might allow for more rapid implementation of interventions7 (7).In another study, steroids were reported to be more effective than immunoglobulin(12).
However, the difference in the efficacy between steroid and immunoglobulin is difficult to explain at present(18). Even though these two treatments were used in children with ADEM, neuromyelitis optica, or other immune mediated brain disorders and are equally effective.
Neonatal and very young infants with pertussis often show severe clinical course with apnea, seizures, and encephalopathy, resulting in the highest mortality among all age group. Avoiding transmission to this age range of patients should be strongly encouraged. Centers for Disease Control and Prevention (CDC) recommend pertussis vaccination for all babies and children, preteens and teens, and pregnant women. However, Japanese immunization program does not recommend additional boosters for adolescents, pregnant women, and adults (19). The resurgence of pertussis should stimulate new research to develop vaccines with greater capacity of protection against current clones.
Cocoon immunization - where both parents are vaccinated in the post-partum period - may offer some protection again infant pertussis infection. Cocoon immunisation could be considered in circumstances where antenatal vaccination of the mother has not occurred (20) .
We believe that a strategy must be implemented in Tunisia to vaccinate adults: cocooning vaccination- to reduce morbidity and mortality secondary to pertussis in children.

CONCLUSION :

This report draws the attention to a serious neurological complication of pertussis infection due to direct invasion of the causative bacteria or its products into the central nervous system. Further analysis of the pathogenesis is needed to determine the optimal treatment. The resurgence of pertussis should stimulate new research to develop vaccines with greater capacity of protection against current clones and also encourage implementation of new strategies for vaccination in order to reduce the risk of disease in infants such as offering pertussis vaccination to all parents of newborns.

REFERENCES :

[1] Guiso, N., & Bassinet, L. (2005). Coqueluche. EMC - Maladies Infectieuses, 2(2), 1–9.

[2] America Academy of Pediatrics Commitee on Infectious Diseases. Prevention of pertussis among adolescents: recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. Pediatrics. 2006 Mar;117(3):965-78.

[3] Surridge J, Segedin ER, Grant CC. Pertussis requiring intensive care. Arch Dis Child. 2007 Nov;92(11):970-5.

[4] Snyder J, Fisher D. Pertussis in childhood. Pediatr Rev. 2012 Sep;33(9):412-20

[5] Guiso, N. (1999). Le diagnostic biologique de la coqueluche : culture, PCR ou sérologie ? Revue Française Des Laboratoires, 1999(314), 29–31.

[6] Munoz JJ, Bernard CC, Mackay IR. Elicitation of experimental allergic encephalomyelitis (EAE) in micewith the aid of pertussigen. CellImmunol. 1984 Jan;83(1):92-100.

[7] Murray EL, Nieves D, Bradley JS, Gargas J, Mason WH, Lehman D, et al. Characteristics of Severe Bordetella pertussis Infection Among Infants <=90 Days of Age Admitted to Pediatric Intensive Care Units - Southern California, September 2009-June 2011. J Pediatr Infect Dis Soc. 1 mars 2013;2(1):1-6.

[8] Kavitha TK, Samprathi M, Jayashree M, Gautam V, Sangal L. Clinical Profile of Critical Pertussis in Children at a Pediatric Intensive Care Unit in Northern India. Indian Pediatr. 2020 Mar 15;57(3):228-231.

[9] Machado MB, Passos SD. Severe pertussis in childhood : update and controversy –systematic review. Rev Paul Pediatr. 2019 Jun 19;37(3):351-362.

[10] ZELLWEGER H. Pertussis encephalopathy. Arch Pediatr (N Y). 1959 Oct;76:381-6.

[11] Grant CC, McKay EJ, Simpson A, Buckley D. Pertussis encephalopathy with high cerebrospinal fluid antibody titers to pertussis toxin and filamentous hemagglutinin. Pediatrics. 1998 Oct;102(4 Pt 1):986-90

[12] Hiraiwa-Sofue A, Ito Y, Mori H, Ichiyama T, Okumura A. Pertussis-associatedencephalitis/encephalopathywithmarkeddemyelination in an unimmunized child. J NeurolSci. 2012 Sep 15;320(1-2):145-8

[13] Fry NK, Duncan J, Wagner K, Tzivra O, Doshi N, Litt DJ, Crowcroft N, Miller E, George RC, Harrison TG. Role of PCR in the diagnosis of pertussis infection in infants: 5 years' experience of provision of a same-day real-time PCR service in England and Wales from 2002 to 2007. J Med Microbiol. 2009 Aug;58(Pt 8):1023-1029.

[14] Waters V, Jamieson F, Richardson SE, Finkelstein M, Worm sbecker A, Halperin SA. Outbreak of atypical pertussis detected by polymerase chain reaction in immunized preschool- aged children. Pediatr Infect Dis J. 2009 Jul;28(7):582-7.

[15] Heininger U. Update on pertussis in children. Expert Rev Anti Infect Ther. 2010 Feb;8(2):163-73.

[16] Dierig A, Beckmann C, Heininger U. Antibiotic treatment of pertussis: are 7 days really sufficient? Pediatr Infect Dis J. 2015 Apr;34(4):444-5

[17] Ichiyama T, Shoji H, Kato M, Sawaishi Y, Ozawa H, Matsubara T, Furukawa S. Cerebrospinal fluid levels of cytokines and soluble tumour necrosis factor receptor in acute disseminated encephalomyelitis. Eur J Pediatr. 2002 Mar;161(3):133-7

[18] Halperin SA, Vaudry W, Boucher FD, Mackintosh K, Waggener TB, Smith B;Pediatric Investigators Collaborative Network on Infections in Canada. Is pertussis immune globulin efficacious for the treatment of hospitalized infants with pertussis? No answer et. Pediatr Infect Dis J. 2007 Jan;26(1):79-81

[19] Takajo D, Nonoyama S. Severe pertussis in a young infant due to household transmission: the needs of pertussis vaccination boosters in Japan. Clin Case Rep. mai 2018;6(5):810-2.

[20] Cherry JD, Doust mohammadi S. Pertussis vaccines.CurrOpinPediatr.2022Apr1;34(2):126-131.