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BRAIN ABSCESS BY CITROBACTER DIVERSUS IN INFANCY

CASE REPORT

RUBENS FEFERBAUM, EDNA M. A. DINIZ**, MARCELO VALENTE*, CLÁUDIA R. GIOLO*** ,RENATA A. VIEIRA***, ANA L. S. GALVANI*, MARIA E. J. CECCON*, MARIA C. K. ARAUJO*, VERA L. J. KREBS*, FLÁVIO A. C. VAZ*****

ABSTRACT - *Citrobacter diversus* is closely related to brain abscess in newborn infants. We describe a case of brain abscess by this bacteria in a newborn infant and his clinical and cranial computed tomographic evaluation until the fourth month of life and discuss therapeutic management of this patient.

KEY WORDS: infancy, brain abscess, *Citrobacter diversus.*

Abscesso cerebral por *Citrobacter diversus* na infância: relato de caso

RESUMO - *Citrobacter diversus* é a bactéria mais associada a abscessos cerebrais durante o período neonatal. Descrevemos um caso de abscesso cerebral por esta bactéria em um recém-nascido e sua evolução clínica e tomográfica até o quarto mês de vida. São discutidos aspectos diagnósticos e terapêuticos desta grave infecção do recém-nascido.

PALAVRAS-CHAVE: infância, abscesso cerebral, *Citrobacter diversus.*

Although not common in the neonatal period, brain abscesses have a high mortality rate and appear as complication of neonatal meningitis in 1.3 to 4.0% of patients. In neonates the progression of the disease may be insidious, with clinical manifestations resembling other neurological pathologies of the neonatal period, such as congenital hydrocephalus. The high frequency and death rates of brain abscesses caused by *Citrobacter diversus* makes clear the need for an early diagnosis and treatment.

In this article we discuss the case of an infant with a brain abscess by *Citrobacter diversus*, his outcome, and a review of the literature on this pathology.

CASE

GRT, 47 days old, male, admitted in the neonatal intensive care unit (NICU) in 07/27/97. Obstetrical history: full term infant, uncomplicated gestation, delivered by elective cesarean section with unruptured membranes, Apgar scores of 9 (1st minute) and 9 (5th minute). Personal history: birth weight 3,420 g, height 48 cm, head circumference (HC) 34 cm, thoracic circumference 33 cm; discharged from the maternity hospital after 3 days.

Admitted in a pediatric clinic at the age of 46 days, with a one day history of poor feeding, nausea, irritability, lethargy and fever (37.7º C), and signs of respiratory distress, raised anterior fontanel and enlarged HC (42.3 cm). A complete blood count was done with hemoglobin level 7,0 g/dl, hematocrit 21%, white blood cell count (WBC) 14,900/mm^3 with 80% neutrophils (9% band cells) in the differential. A spinal tap was performed

Unidade de Cuidados Intensivos Neonatais(UCINE) do Instituto da Criança "Prof. Pedro de Alcântara" de Hospital das Clínicas (HC) da Faculdade de Medicina da Universidade de São Paulo (FMUSP): *Doutor(a) em Pediatria pela FMUSP e Médico(a) Assistente de Instituto da Criança HC/FMUSP; **Professora Livre-Docente em Pediatria Neonatal da FMUSP e Chefe da UCINE; ***Médica Estagiária da UCINE; ****Professor Titular de Pediatria da FMUSP. Aceite: 18-abril-2000.

Dr. Rubens Feferbaum - Rua Heitor Penteado, 502 - 05438-000 São Paulo SP - Brasil.

with cerebrospinal fluid (CSF) of turbid appearance, leukocyte count 630,000/mm^3 (20% neutrophils, 75% lymphocytes, 5% monocytes), glucose concentration 13 mg/dl, protein concentration 67 mg/dl, and negative Gram stain. The initial treatment included ampicillin (300 mg/kg/day), ceftriaxone (100 mg/kg/day) and dexamethazone (0.6 mg/kg/day). The patient was transferred to the NICU of the São Paulo University Children's Hospital on the following day.

On the second day after admittance the CSF still appeared turbid, with 2,400/mm^3 erythrocytes, 1520 WBC/mm^3, 78% neutrophils, 4% lymphocytes, 15% monocytes, 1% eosinophils, 2% macrophages, 475 mg/dl protein and 17 mg/dl glucose. The Gram stain and the bacterial culture were both negative. A cranial computed tomography (CT) scan detected multiple lesions in the left frontal region, suggesting brain abscesses, with areas of low attenuation in the white matter of both frontal lobes. Also present were small areas of intracavitary hemorrhage, with midline shifting to the right.

Aspiration of the brain abscess removed a thick dark brown purulent liquid with putrid odor, with positive staining for Gram-negative bacilli and a large number of polymorphonuclear leukocytes. Bacterial culture from this sample was positive for *Citrobacter diversus*, with antibiotic sensitivity to ceftriaxone and metronidazole, which was added to the therapeutic scheme. Due to antibiotic resistance, ampicillin was then removed from use. Multiple aspirations were required during the first week in order to drain the abscesses and reduce intracranial pressure .

On day 11, there was a deterioration of the clinical condition, with signs of septic shock and raised intracranial pressure (tense anterior fontanel measuring 6x5 cm, HC 42.8 cm). A new aspiration of the abscess was performed, still showing the presence of *Citrobacter diversus*. On this occasion, the antibiotic treatment was modified, changing ceftriaxone for ceftazidime (150 mg/kg/day) and with the addition of vancomycin (40 mg/kg/day) due to a possible secondary infection by Gram-positive bacteria. With the new treatment scheme, there was a sustained improvement of the clinical condition and control of the intracranial pressure. CT scan on day 21 displayed a slight reduction of the abscess and a reduction of the midline shifting.

Electroencephalography performed on day 5 and 30 displayed focal epileptiform activity projecting on the left frontal region. Brainstem auditory evoked potentials displayed a left neurosensory deafness.

On day 56, after completion of 6 weeks of antibiotic therapy, the patient was discharged, with oral phenobarbital 3 mg/kg/day as anticonvulsive treatment. During outpatient following, the child presented frequent clonic seizures with organized jerks of the upper limbs, requiring the change from phenobarbital to valproic acid for control of the convulsions. A CT scan performed at the age of 4 months displayed a marked improvement of the brain lesions.

DISCUSSION

Neonatal meningitis when caused by *Citrobacter diversus* or *Proteus mirabilis* is complicated by abscess formation in 40 to 70% of patients[1,2]. Approximately 15 to 20% of Gram-negative bacterial meningitis are complicated by abscess.

The clinical manifestations of brain abscess in newborn infants are those of infection and intracranial hypertension (vomiting, raised fontanel, dysjunction of cranial sutures and enlargement of the head circumference)[3]. In the case reviewed here, the progression of the disease has probably been insidious, since the symptoms raised only concern themselves with 46th days of age. By that time, head circumference was already above de 95th percentile, suggesting hydrocephalus. The clearly marked lesions present in the first CT scan performed (Fig 1) could only develop before the onset of the symptoms described.

Routine laboratory studies are usually not particularly helpful in the diagnosis of brain abscess. CSF findings are nonspecific, being either normal or resembling a bacterial meningitis. As with this patient, Gram staining and bacterial culture are usually negative. The extremely marked pleocytosis and low glucose seen in the patient's first CSF samples usually occur in the rupture of the abscess capsule[3,4].

Early diagnosis of brain abscess is possible with the availability of modern neuroimaging tools. The use of cranial ultrasonography is possible in children with an open anterior fontanel, with the abscess appearing as a central hypoechoic region with well-marked borders, making possible an

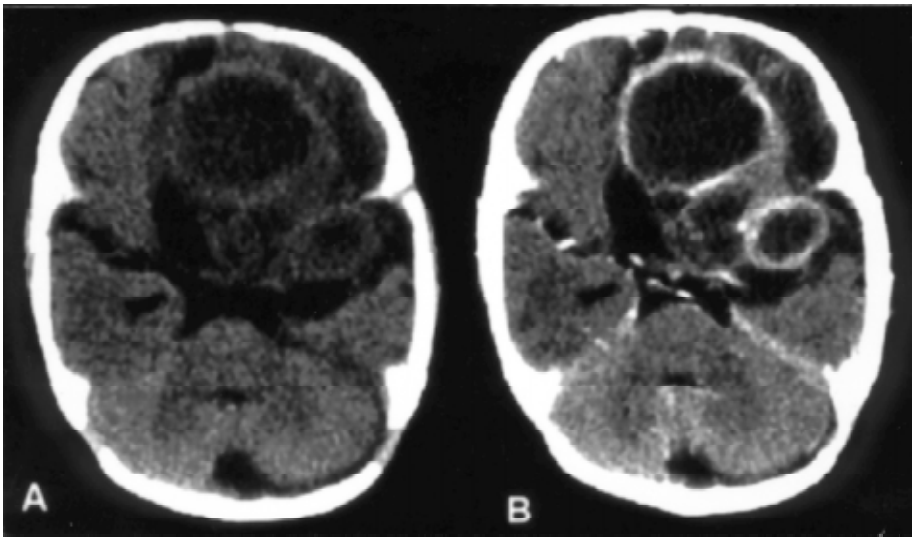

Fig 1. Initial unhanced CT scan (A) and after iodine contrast enhancement (B). Rounded expansive formations with a central low-density component and a ring-like contrast-enhancing periphery, shown in the frontal and temporal regions of the left hemisphere. The multiple lesions are responsible for the midline shifting to the right with subfalcine herniation.

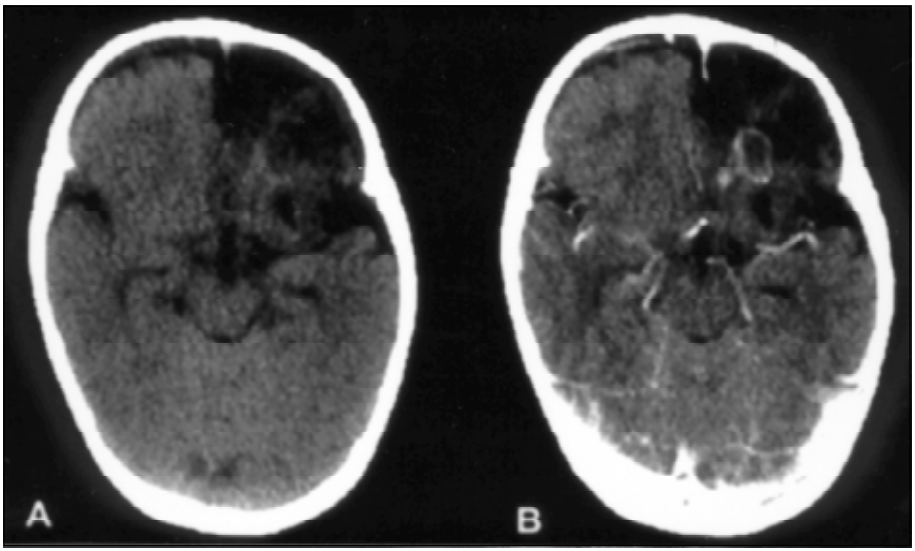

Fig 2. Unhanced CT scan (A) and after iodine contrast (B) performed 4 months after the beginning of treatment. There are areas of retraction in the left frontal temporal region. The presence of contrast-enhancing regions at this stage is probably related to vascular abnormalities with alteration of the blood-brain barrier and to cerebral infarction. There is no organized abscess present.

aspiration under stereotactic guidance. Definitive diagnostic studies are CT scanning, magnetic resonance imaging (MRI) and radionuclide scanning of the brain. Although less sensitive than MRI, CT scanning remains as the best suited tool for evaluation, permitting serial examinations of a patient with brain abscess with a high degree of sensitivity and good image resolution[5], as seen in Figures 1 and 2 .

The most common etiologic agents of brain abscesses in the neonatal period are Gram-negative bacteria, most frequently *Citrobacter diversus, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens* and other *Enterobacteriaceae*[4,6]. Gram-positive bacteria like *Staphylococcus sp.* are uncommon[5]. The role of fungi, mainly *Candida* sp, as an etiologic agent has been increasingly important, especially in very-low-birth-weight infants [7].

Citrobacter diversus is a Gram-negative enteric bacillus, a pathogen from the gastrointestinal tract, from the *Enterobacteriaceae* family and *Salmonella arizona* genus. The infection of the central nervous system (CNS) by this agent usually leads to intense vasculitis, cerebritis and cerebral infarction. The infected necrotic tissue then becomes the site of abscess formation, either isolated or multiple, as it occurs in up to 77% of the reported cases of *Citrobacter diversus* meningitis[3,4,8].

As a nosocomial pathogen, *Citrobacter diversus* can be isolated, and remain for years, in the environment of newborn services, or in the gastrointestinal tract of the staff involved with neonatal care. A vertical form of transmission is possible but unlikely. Epidemic outbreaks in neonatal services, when present, are mostly related to the transmission from the hands of the hospital staff[6].

Recent research in the profile of plasmids and reverse endonuclease obtained from *Citrobacter* chromosomes has been used as an epidemiological marker for infections. In 1992, Morgan et al. managed to isolate through endonuclease analysis the same strain of *Citrobacter* in the blood and CSF of two infants born nine months apart in a Scottish maternity, thus proving the colonization of the neonatal ward by that bacteria[8].

The therapy of choice for brain abscess in infants requires both antibiotic and surgical drainage by guided aspiration or excision.

The choice of antimicrobial therapy is based on bacterial susceptibility and CNS penetration of the drug. Most strains (97%) of *Citrobacter diversus* are resistant to ampicillin and penicillin. There is a good sensitivity for aminoglycosides, but those have poor CNS penetration. Third-generation cephalosporins are usually the first choice of treatment, with the use of imipenem-cilastatin or meropenem as a good alternative[3,6,11]. Generally, a broad-spectrum combination of agents must be employed. In our patient a good response was obtained with the association of ceftazidime, metronidazole and vancomycin.

Surgical drainage of the abscess is usually required. Aspiration of the abscess or excision are the surgical techniques available and neither has been proven superior. Aspiration, usually performed with stereotactic ultrasound guidance in neonates, is usually preferred due to the low morbidity and mortality from brain injury and the ability to obtain samples for staining, culture and histology. When the clinical condition is critical, the progression unsatisfactory or the aspiration of the abscess not possible, a surgical excision is recommended. Excision provides the definitive treatment of cerebral abscess, but this method remains controversial due to the possibility of rupture into the ventricular system and dissemination of the infection[10,11]. Our patient was subjected to three full aspirations of multiple abscesses, with the presence of purulent material on each occasion.

In our patient, a sustained clinical improvement was reached after the aspiration of the abscesses and the introduction of the ceftazidime/metronidazole/vancomycin antibiotic scheme. This scheme was maintained for six weeks with good results. During his follow-up at the outpatient clinic up to the age of 4 months, he remained in a good clinical condition. In spite of the neurological sequels and the altered CT scan (Fig 2), his neuropsychomotor development was compatible with his age.

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