HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb

Document heading

Neurobrucellosis in children

Mohamed Ata Hendaus*, Rasha Muneer Qaqish, Ahmed Hassan Alhammadi

Department of Pediatrics, Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar

ARTICLE INFO

Article history:
Received 6 Nov 2014
Received in revised form 21 Nov 2014
Accepted 24 Nov 2014
Available online 28 Nov 2014

Keywords:
Children
Brucella
Neuro

ABSTRACT

Neurobrucellosis is a complication of brucellosis, which is considered endemic in the Indian subcontinent, Arabian Peninsula and Mediterranean countries. *Brucella* reaches the central nervous system via hematogenous spread in the infected human being, or through phagocytosis. Neurobrucellosis can present with any neurological symptoms, hence, the index of suspicion must be high enough to make proper diagnosis. Cerebrospinal fluid studies are usually diagnostic, while imagings including magnetic resonance imaging and computed tomography are of little assistance. As for therapy, a combination of antibiotics must be administered with a goal to reduce relapse or avoid failure. The duration of treatment should be tailored as per clinical signs and symptoms until the cerebrospinal fluid components return to normal, which might be up to six months. In this article, we present an overall view of current understanding of neurobrucellosis in children, its epidemiology, clinical features, diagnostic tests, and management options.

1. Introduction

Human brucellosis, also known as Malta or undulant fever, results from infection by bacteria of genus *Brucella*[1]. Neurobrucellosis is a complication of brucellosis[2]. Human beings acquire the infection by ingesting infected milk or milk products. In addition, contact with infected animals, such as goats, camels, sheep, swine and cattle could result in the infection[3].

The first identification of the *Brucella* genus was by Bruce in 1887 in an autopsy in Malta. Gul reported the first case of neurobrucellosis in 2009 eventually[4].

Brucella species are small, non-motile, non-encapsulated, slow-growing, Gram-negative and facultative coccobacilli[5]. The species that infect human beings are *Brucella canis*, *Brucella melitensis* (*B. melitensis*), *Brucella abortus*, and *Brucella suis*, while *Brucella ovis* and *Brucella neotomae* do not[1]. Brucellosis is considered as a common zoonotic infection in the Middle East, South and Central Asia, South and Central America, North and East Africa as well in the Mediterranean countries of Europe[6]. In particular, *B. melitensis* is considered endemic in the Indian subcontinent, Arabian Peninsula and Mediterranean countries[7]. The incubation period for the organism ranges from few days to several months, but the majority of infected individuals show signs of illness within 3 to 4 weeks[8].

2. Epidemiology

There are more than 500 000 new cases of brucellosis reported annually worldwide[9]. In the endemic areas of the United States, there is around 1 case per 1 000 people per year while in the United Kingdom it is 0.3 cases per million people[6]. In endemic areas such as Kuwait, Saudi Arabia and Peru, there are around 200 cases of brucellosis per 100 000 populations[10].

In Turkey, there is an estimated 18 000 new cases of brucellosis per year with sero-positivity rate of 2.6%-14.4% among Turkish people[11]. The overall frequency of neurobrucellosis ranges from 0.5% to 25.0%[2,3]. The prevalence of neurobrucellosis in adolescents is less than 5.0%[12,13], while in children ranges from less than 1.0% to 2.2%[14]. The overall mortality rate of neurobrucellosis ranges from 0.0% to 27.0%[2,3,15]. There is no

*Corresponding author: Mohamed Ata Hendaus, MD, FAAP, Department of Pediatrics, Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar.
Tel: +974-4439-2239
Fax: +974-4443-9571
E-mail: mhendaus@yahoo.com
Foundtion Project: Supported by Hamad Medical Corporation (Ref. No. 14447/14) who provided 7 000 Qatari rial.

clear neurobrucellosis predisposition for patients with underlying diseases[3]. Gender predisposition to the disease is debatable. The usual documented ratio is two males to one female, however in Saudi Arabia the ratio is reported as two females to one male[7].

3. Pathogenesis

The exact mechanism of how *Brucella* reaches the central nervous system (CNS) is still unknown[3]. It might reach the CNS via hematogenous spread in the infected human being[1], or through phagocytosis since *Brucella* is usually adapted to the intracellular setting[3]. Previous studies showed that VirB operon, a type IV secretion pathway that is induced on phagosomal acidification, could be the culprit in initiating the pathogenesis[16,17].

Other studies showed that *Brucella* may cause cytotoxic damage to the cerebral white matter through its endotoxins and hence might lead to demyelination[2,18]. Watanabe *et al.* mentioned in their study that a lipo-oligosaccharide of *B. melitensis* had a ganglioside-like structure that can induce anti-GM1 ganglioside antibodies resulting in symptoms similar to Guillain-Barré. This study was conducted on mice[19].

4. Clinical features

Neurobrucellosis can present with any neurological symptoms[1], hence, the index of suspicion must be high enough to make proper diagnosis[20].

Tuberculosis and syphilis might present similar to neurobrucellosis[1]. In children, the presentation is usually acute as compared to adults[14].

Patients with neurobrucellosis present with diffuse CNS involvement and/or peripheral neuropathy or radiculopathy[3]. The CNS manifestations include headache[4,21], agitation[22], neck stiffness[7], myelitis manifested by back pain[3,4], spastic paraparesis[3], seizures especially if there is underlying cerebral venous sinus thrombosis[23], and acute meningitis or meningoencephalitis[24]. In addition, diabetes insipidus, blindness, and optic neuritis have been reported[25-28]. Patients with peripheral neuropathy or radiculopathy present with back pain, paraparesis, areflexia[3], and hypoesthesia[4]. Neurobrucellosis might also manifest with disorientation, apathy[22], psychosis, depression, euphoria and personality disorders[2].

5. Diagnosis tests

The following are the recommendations for proper diagnosis of neurobrucellosis:

*Neurological manifestations not related to other diseases[2].

*Cerebrospinal fluid (CSF): lymphocytic pleocytosis are often seen in 91% of cases of *Brucella* meningitis[1,2]. The CSF protein is usually raised[1,2], and glucose could be normal or low[1]. In cases where neurobrucellosis affect the cerebellum, the protein concentration is elevated but there is no leukocytosis[3].

*CSF positive culture for *Brucella* is usually diagnostic[1], however, CNS culture is frequently sterile[3]. Only around 30% of patients with neurobrucellosis had positive blood culture and 14% had positive CSF culture[4]. Moreover, ELISA might be an indispensable tool in obtaining antibody against *Brucella* in the CSF[1]. Alternatively, positive *Brucella* IgG agglutination titer in the blood is used as part of the diagnostic criteria[2].

*Response to appropriate antibiotic use with a drop in the protein and lymphocyte count in the CSF[2].

6. Imaging

The neuroimaging manifestations of neurobrucellosis do not always match the clinical picture[29], and could be non-specific[1]. Computed tomography (CT) or magnetic resonance imaging is usually required[30], but their neuroimaging appearance usually shows a non-specific inflammatory process[1,29], similar to other bacterial meningitides[1]. However, CT can rarely show thickening of the optic nerves, dilatation of the lateral ventricle(s), cerebral atrophy or cerebellar abscess[24].

CT or plain radiograph of the spine is usually ordered but imaging usually does not differentiate between spinal brucellosis and pyogenic osteomyelitis or tuberculous spondylitis[1]. In addition, white matter changes in neurobrucellosis may resemble multiple sclerosis, acute disseminated encephalomyelitis, or Lyme disease[31].

7. Management options

The literature lacks consensus regarding the antibiotic choice in cases of neurobrucellosis, but it reaches an agreement that a combination of antibiotics must be administered[15,24], with a goal to reduce relapse or avoid failure[24].

The commonly used regimen is co-trimoxazole plus rifampicin or doxycycline, which is considered effective with low relapse rates[32]. Other regimens include doxycycline, rifampicin and ceftriaxone[4,6,33], or trimethoprim-sulfamethoxazole[34,35].

A Turkish study showed a preference towards the ceftriaxone-based regimen since its course is shorter and more effective[36]. The American Academy of Pediatrics recommends the use of gentamicin for the initial 7 to 14 d of antibiotics treatment, added to rifampin and tetracycline for a minimum of six weeks up to six months, depending on the clinical and CSF response; if tetracyclines are not used, then trimethoprim-sulfamethoxazole is an alternative[8].

In general, the duration of treatment should be tailored as per