Pathophysiology of neonatal acute bacterial meningitis

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Neonatal meningitis is a severe acute infectious disease of the central nervous system and an important cause of morbidity and mortality worldwide. The inflammatory reaction involves the meninges, the subarachnoid space and the brain parenchymal vessels and contributes to neuronal injury. Neonatal meningitis leads to deafness, blindness, cerebral palsy, seizures, hydrocephalus or cognitive impairment in approximately 25–50% of survivors. Bacterial pathogens can reach the blood–brain barrier and be recognized by antigen-presenting cells through the binding of Toll-like receptors. They induce the activation of NFκB or mitogen-activated protein kinase pathways and subsequently upregulate leukocyte populations and express numerous proteins involved in inflammation and the immune response. Many brain cells can produce cytokines, chemokines and other pro-inflammatory molecules in response to bacterial stimuli, and polymorphonuclear leukocytes are activated, activated and released in large amounts of superoxide anion and nitric oxide, leading to peroxynitrite formation and generating oxidative stress. This cascade leads to lipid peroxidation, mitochondrial damage and breakdown of the blood–brain barrier, thus contributing to cell injury during neonatal meningitis. This review summarizes information on the pathophysiology and adjuvant treatment of acute bacterial meningitis in neonates.

Introduction

Meningitis is the most frequent and serious infection of the central nervous system (CNS) and affects the pia matter, arachnoids and subarachnoid space (van de Beek et al., 2004). It is an important cause of morbidity and mortality worldwide, principally in neonates and children (Grandgirard & Leib, 2010), with the impact varying according to the geographical location of the patient and the causative organism (Kim, 2003).

Neonatal meningitis occurs beyond 28 days of life (Nizet & Klein, 2011). Several studies conceptualize the neonatal period as up to 30- or 90-days-old (Furyk et al., 2011). Bacterial meningitis is a severe infectious disease, with mortality rates varying between 10% and 15% (Gaschignard et al., 2011), and the incidence is described as 0.25–6.1 per 1000 live births (developed countries 0.3; Asia 0.48–2.4; Africa and South Africa 0.81–6.1) (Heath & Okike, 2010). In a systematic analysis of mortality estimates...
in 2010 with time trends since 2000, 7.6 million deaths were reported to occur in children younger than 5 years old in 2010, with 64.0% (4,879 million) of these attributable to infectious causes and 40.3% (3,072 million) occurring in neonates. Of these neonatal deaths, 5.2% (0.393 million) were a result of sepsis or meningitis (Liu et al., 2012). The major pathogens are *Streptococcus agalactiae* and *Escherichia coli* K1, which cause at least two-thirds of all deaths from neonatal meningitis in Europe (Heath et al., 2011; Holt et al., 2001). Other Gram-negative bacteria implicated include *Klebsiella, Enterobacter*, *Citrobacter* and *Serratia* species. (Heath et al., 2011). The remaining causes include *Streptococcus pneumoniae* (6% of cases) and *Listeria monocyto genes* (5% of cases) (Heath & Okike, 2010).

The early- and late-onset patterns of the disease have been associated with systemic bacterial infections during the first month of life. Many studies define early-onset bacterial infection as an infection that occurs in the first 72 h of life; others define it as an infection that occurs in the first 5 or 6 days of life (Remington, 2011). Group B streptococcal infection in neonates and young infants is classified by age at onset (Kim, 2003). Early-onset infection with *Streptococcus agalactiae* generally presents at or within 24 h of birth (Heath & Okike, 2010), but can occur through day 6 of life (Puopolo & Baker, 2012). Late-onset disease has been variably defined for epidemiological purposes as occurring after 72 h to 6 days of life; late-onset infection can manifest after the first week to months after birth as sepsis and meningitis or other focal infections (Remington, 2011). Late-onset infection with *Streptococcus agalactiae* usually occurs at 4–5 weeks of age (range: 7–89 days) (Puopolo & Baker, 2012). Early-onset meningitis is more likely to be caused by *Streptococcus agalactiae*, *E. coli* and *L. monocytogenes*, while late-onset meningitis may be caused by *Streptococcus agalactiae*, *E. coli*, *L. monocytogenes*, Gram-negative organisms, *Staphylococcus* spp. (Heath et al., 2003) and *Streptococcus pneumoniae* (Kim, 2008).

Newborns are especially vulnerable to infection. The cellular and humoral immunities are immature, including the phagocytic function (Filias et al., 2011; Pong & Bradley, 1999). A full-term newborn has a distinct innate immune system that is biased towards T-helper type 2/T-helper type 17-polarizing and anti-inflammatory cytokine production, with relative impairment in T-helper type 1-polarizing and cytokine production. The deficient expression of complement and of antimicrobial proteins and peptides likely contributes to a newborn’s susceptibility to pyogenic bacteria (Cuenca et al., 2013). The phagocytic ability of the neutrophils and monocytes of 42 neonates has been evaluated by the intake of *E. coli* by phagocytes (Filias et al., 2011). The phagocytic ability was impaired at birth in pre- and full-term neonates compared with adults. This defect was transient, with the phagocytic ability in neonates reaching the same level as that of adults 3 days after birth. It is widely believed that the development of the blood–brain barrier (BBB) proceeds from late gestation and continues through the postnatal period, and it may be a time of increased permeability that renders the developing brain more vulnerable (Zeng et al., 2011). Other authors have affirmed that adult mechanisms and functionally effective tight junctions are present in the embryonic brain and that some transporters are more active during development than in the adult brain (Ek et al., 2012). Developing cerebral vessels appear to be more fragile than in adults and more susceptible to drugs, toxins and pathological conditions, thus contributing to cerebral damage and later neurological disorders. After birth, the loss of defence by efflux transporters in the placenta can contribute to cerebral damage and later neurological disorders in the neonatal brain because it is more defenceless than the fetal brain (Saunders et al., 2012).

Because of these neonatal particularities, bacterial meningitis can cause acute complications involving the brain parenchymal vessels (vasculitis), ventriculitis, systemic complications (including pneumonia) and septic shock, which contribute to an unfavourable outcome (Sellner et al., 2010). Long-term neurological sequelae, including deafness, blindness, cerebral palsy, seizures, hydrocephalus or cognitive impairment, present in approximately 25–50% of survivors (de Louvois et al., 2005).

**CNS bacterial invasions**

**Initial bacterial entry into the CNS**

Early-onset infections are acquired vertically through exposure to the micro-organism via the mother’s genital tract (Remington, 2011). Neonatal infection occurs primarily when micro-organisms ascend from the vagina to the amniotic fluid after the onset of labour or rupture of the membranes, although *Streptococcus agalactiae* can invade through intact membranes (Verani et al., 2010). *Streptococcus agalactiae* can be aspirated into the fetal lungs and might be transferred haematogenously into the CNS (Pong & Bradley, 1999). The bacteria can cross the BBB by different mechanisms: via transcellular or paracellular traversal and in infected phagocytes. Transcellular traversal occurs when the micro-organism penetrates the cells without any evidence in the cells or intracellular tight-junction disruption (Kim, 2008). *Streptococcus pneumoniae, Streptococcus agalactiae* and *E. coli* can all cross the BBB via this mechanism (Kim, 2003). To cross the BBB, *Streptococcus pneumoniae* must interact with cell wall phosphorylcholine and platelet-activating factor receptor (Kim, 2008). *Streptococcus agalactiae* crosses the BBB with the aid of the lipoprotein laminin-binding protein (Tenenbaum et al., 2007). *L. monocytogenes* crosses the BBB by microbial penetration using transmigration within infected phagocytes; this mechanism is known as a Trojan horse (Kim, 2008).

**Bacterial recognition and immune response**

Micro-organisms can replicate within the subarachnoid space concomitantly with the release of bacterial products,
such as peptidoglycan and cell wall fragments, which are highly immunogenic and can lead to an increased inflammatory response in the host (Sellner et al., 2010). These compounds are recognized by antigen-presenting cells through binding to pattern-recognition receptors such as Toll-like receptors (TLRs), a nucleotide-binding domain leucine-rich repeat (NLR) region-containing family of proteins (Mook-Kanamori et al., 2011).

Nucleotide-binding oligomerization domain-2 (NOD2) is activated by cell wall peptidoglycan (Liu et al., 2010; Opitz et al., 2004). NOD2 has a critical role in the establishment of the lethal inflammation associated with streptococcal meningitis through activation of the transcription factor NFkB and production of inflammatory cytokines (Mook-Kanamori et al., 2011), as have been demonstrated in murine microglia and astrocyte cells (Liu et al., 2010). The NLR family, pyrin-domain-containing 3 (NLRP3) and the absent in melanoma 2 (AIM2) inflammasomes are activated by exotoxin pneumolysin and DNA bacteria in pneumococcal infection, respectively, which mediates the cleavage of pro-IL-1β into mature IL-1β (Koppe et al., 2012). Streptococcus agalactiae activates NLRP3 through the expression of β-haemolysin, an important virulence factor (Costa et al., 2012). NLRP3 has been implicated in responses to Staphylococcus aureus, L. monocytogenes, Klebsiella pneumoniae and E. coli (Davis et al., 2011).

Eleven TLR family members have been described in humans. These are separated into two broad categories: members of one group are expressed at the cell surface for extracellular ligand recognition, while members of the other group are localized in the endosomal compartment to recognize pathogen nucleic acids (Hanke & Kielian, 2011). TLRs 1–9 are expressed in microglia cells, whereas astrocytes express TLRs 2, 3 and 9. Neurons express TLRs 3, 7, 8 and 9. Oligodendrocytes express TLRs 2 and 3. Streptococcus pneumoniae bacterial compounds, including peptidoglycans and lipoteichoic acids, are recognized in the CNS by TLR2 (Mitchell et al., 2010). The exotoxin pneumolysin is recognized by TLR4 (Malley et al., 2003) and the bacterial DNA is recognized by TLR9, which is an intracellular pattern-recognition receptor activated by CpG (cytosine-phosphate-guanine) (Hemmi et al., 2000). E. coli interacts through toxin lipopolysaccharide with TLR4 (Rivest, 2003). In vitro, L. monocytogenes cell wall components such as lipoteichoic acids are recognized by TLR2 with the help of CD14 and TLR6 (Flo et al., 2000; Janot et al., 2008; Seki et al., 2002). The protein flagellin interacts through TLR5 (Hayashi et al., 2001). Streptococcus agalactiae interacts with TLR2 through lipoteichoic acid and through the engagement of TLR7 and/or TLR8 by microbial RNA (Mook-Kanamori et al., 2011) (Table 1).

TLRs are essential to trigger the immune response during meningitis, signalling the production of key inflammatory mediators (Fig. 1) (Hanke & Kielian, 2011).

The majority of TLRs utilize a common intracellular adaptor protein known as myeloid differentiation factor 88 (MyD88) (Koedel, 2009). MyD88 is associated with IL-1 and IL-1 receptor-associated kinase-4 (IRAK4), which is a serine/threonine kinase that plays an essential role in signal transduction by Toll/IL-1 receptors (Wang et al., 2006). Subsequently, IRAK interacts with TNF and the TNF receptor-associated factor family and provides a link to NFkB-inducing kinase, resulting in the release and nuclear translocation of NFkB (Hanke & Kielian, 2011). The NFkB family comprises a closely associated family of transcription factors, which play a key role in the expression of genes that have been implicated in the development of accessory cell and leukocyte populations and in the expression of many proteins involved in inflammation and the immune response (Tato & Hunter, 2002). NFkB is a transcriptional activator of various genes involved in the pathogenesis of meningitis, such as TNF-α, IL-1β, inducible nitric oxide synthase and intercellular adhesion molecules (Fig. 2) (Kastenbauer et al., 2004; Koedel et al., 2000).

Neuronal inflammation
Initial immune response

Knowledge of the pathophysiology of bacterial meningitis in neonates is predominantly based on observations of human patients and studies with experimental animal models (Grandgirard & Leib, 2010). A relative comparison of the ages and stages of human versus rat development has shown that the neonatal period for rats is from birth until day 10 of life (Andersen, 2003).

Many brain cells, such as astrocytes, glial cells, endothelial cells, ependymal cells and resident macrophages, can produce cytokines and pro-inflammatory molecules in response to bacterial replication and its components (Kronfol & Remick, 2000). In a study with 54 human newborns (30 with meningitis and 24 controls), increased levels of TNF-α, IL-1β and IL-6 were detected in the cerebrospinal fluid (CSF) of all of the newborns with meningitis (Krebs et al., 2005). Elevated levels of pro-inflammatory mediators in the CSF are normally found in patients with bacterial meningitis (Lahtz et al., 1998; van Furth et al., 1996). In animal models, administration of TNF-α into the CSF and intravenously has been reported to cause changes that are characteristic of bacterial meningitis and lead to BBB breakdown (Rosenberg et al., 1995; Tsao et al., 2002). TNF-α is a marker of an acute inflammatory response in children with bacterial meningitis (Mukai et al., 2006) and is essential for an adequate host immune response (Aas et al., 2005). IL-1β is an important cytokine that has potent stimulatory effects on white blood cells and promotes the adhesion of neutrophils and monocytes in endothelial cells (Ostergaard et al., 2004). In a study of 21 patients with bacterial meningitis, endothelial-derived adhesion molecules were associated with the extent of CSF pleocytosis and with concentrations of the pro-inflammatory cytokines IL-1β and TNF-α in CSF (Fassbender et al., 1997).
Table 1. Bacterial components and TLRs

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>TLR agonist</th>
<th>TLR</th>
<th>Expression of TLR family members in CNS cells</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Peptidoglycan</td>
<td>2</td>
<td>Microglia, astrocytes, oligodendrocytes</td>
</tr>
<tr>
<td></td>
<td>Lipoteichoic acid</td>
<td>2</td>
<td>Microglia, astrocytes, oligodendrocytes</td>
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<tr>
<td></td>
<td>Pneumolysin</td>
<td>4</td>
<td>Microglia</td>
</tr>
<tr>
<td></td>
<td>Bacterial CpG DNA</td>
<td>9</td>
<td>Microglia, astrocytes, neurons</td>
</tr>
<tr>
<td></td>
<td>Triacylated lipoprotein</td>
<td>1/2</td>
<td>Microglia</td>
</tr>
<tr>
<td></td>
<td>Diacylated lipoprotein</td>
<td>2/6</td>
<td>Microglia</td>
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<tr>
<td><em>E. coli</em></td>
<td>Lipopolysaccharide</td>
<td>4</td>
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<td>Triacylated lipoprotein</td>
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<td>Microglia</td>
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<td><em>L. monocytogenes</em></td>
<td>Lipoteichoic acid</td>
<td>2</td>
<td>Microglia, astrocytes, oligodendrocytes</td>
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<td></td>
<td>Flagellin</td>
<td>5</td>
<td>Microglia</td>
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<tr>
<td></td>
<td>Triacylated lipoprotein</td>
<td>1/2</td>
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<td>Diacylated lipoprotein</td>
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<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>Lipoteichoic acid</td>
<td>2</td>
<td>Microglia, astrocytes, oligodendrocytes</td>
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<tr>
<td></td>
<td>Microbial RNA</td>
<td>7/8</td>
<td>Microglia, neurons</td>
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<tr>
<td></td>
<td>Triacylated lipoprotein</td>
<td>1/2</td>
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<tr>
<td></td>
<td>Diacylated lipoprotein</td>
<td>2/6</td>
<td>Microglia</td>
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</tbody>
</table>

Fig. 1. Pathophysiology of acute bacterial meningitis. The micro-organism adheres to endothelial cells and may breach the BBB and be recognized by antigen-presenting cells through the binding of TLRs. TLRs induce the activation of an inflammatory cascade and express numerous proteins involved in inflammation and the immune response. FLY, flagellin; β-HLY, β-haemolysin; Lmb, lipoprotein laminin; LPS, lipopolysaccharide; LTA, lipoteichoic acid; PGL, peptidoglycan; PAF, platelet-activating factor receptor; PLY, pneumolysin; PRC, phosphorylcholine.
IL-6 has predominantly pro-inflammatory effects such as fever, leukocytosis and the potent induction of acute-phase proteins (Gruol & Nelson, 1997), including the synthesis and secretion of C-reactive protein, serum amyloid A, fibrinogen, ar-antitrypsin, q-antichymotrypsin and haptoglobin (Castell et al., 1989). IL-6 acts as an anti-inflammatory cytokine, and a lack of IL-6 enhances the inflammatory response and decreases vascular permeability in bacterial meningitis (Paul et al., 2003). In animal model studies, we determined that TNF-\(\alpha\), IL-1/\(\beta\), cytokine-induced neutrophil chemoattractant 1 (CINC-1) and IL-6 levels were increased prior to BBB breakdown, and that this breakdown occurred in the hippocampus and in the cortex after the induction of neonatal pneumococcal meningitis (Barichello et al., 2012a) and Streptococcus agalactiae meningitis (Barichello et al., 2011). We suggest that these cytokines are produced at the site of inflammation and play an important role in neutrophil infiltration.

Later neutrophil-mediated response

The production of cytokines leads to the attraction and activation of polymorphonuclear leukocytes and the production of high amounts of reactive oxygen species (Kastenbauer et al., 2002). Sialyl-LewisX on leukocytes binds to P- and E-selectin on endothelial cells. This connection becomes stronger when CXCL8 binds to its specific receptor on neutrophils, triggering the production of integrins lymphocyte function-associated antigen 1 (LFA-1) and CX3 (mac-1). Inflammatory cytokines such as TNF-\(\alpha\) are necessary to induce the expression of intercellular adhesion molecule (ICAM)-1 and -2. The link between endothelial cells and ICAM-1 allows the passage of neutrophils in the direction of the gradient of chemoattractant substances (Fig. 3) (Carlos & Harlan, 1994; Hanna & Etzioni, 2012). This leads to oxidative stress, which in turn leads to cytokine and chemokine activation, enhanced neutrophil activation, lipid peroxidation, DNA single-strand breaks, mitochondrial impairment, tyrosine nitration, matrix metalloproteinase activation and prostaglandin production (Klein et al., 2006). A study with neonatal rats found that protein carbonyls and lipid peroxidation were increased in the hippocampus and cortex during the first hours after pneumococcal and Streptococcus agalactiae meningitis induction (Barichello et al., 2011, 2012a).

Reactive oxygen species and calcium can result in mitochondrial dysfunction, which leads to the release of apoptosis-inducing factor into the cytosol; apoptosis-inducing factor has been reported to be responsible for executing the caspase-independent pathway. Polymorphonuclear leukocytes can also induce the release of cytochrome \(c\) from the mitochondria into the cytosol, resulting in caspase-3 cleavage in a mouse model of pneumococcal meningitis (Mitchell et al., 2004). In children with bacterial meningitis, acrolein-lysine (a marker of lipid peroxidation) and nitrite (a marker of nitric oxide production) have been reported to be several times higher in during the early phase of bacterial meningitis compared with children without meningitis or with aseptic meningitis (Tsukahara et al., 2002). A positive correlation was found between the nitric oxide index and lipid peroxide with white blood cells in the CSF of children with bacterial meningitis (Hamed et al., 2009). These free radicals are highly reactive and may
cause impairment of lipids, proteins, carbohydrates or nucleic acids, thus increasing the risk of sequelae. Because of the high lipid content in the brain and low cerebral antioxidant defences, the CNS is particularly susceptible to the deleterious properties of oxidative stress (de Menezes et al., 2009).

Brain-derived neurotrophic factor (BDNF) is widely distributed throughout the brain and has demonstrated the ability to protect neurons against damage caused by oxidative, metabolic and excitotoxic stress (Marini et al., 2007). BDNF has an important regulatory function in cell proliferation and exerts neuroprotective effects via the modulation of synaptic plasticity by regulating dendritic spines and synaptic density and the expression of synaptic proteins (Abdallah et al., 2013; Tartaglia et al., 2001).

**Novel therapeutic targets in bacterial meningitis**

In neonates with suspected bacterial meningitis, empiric antibiotic treatment should be instituted without delay. In Wistar rats, early antibiotic administration (i.e. 8 h after induction), compared with late antibiotic administration (i.e. 16 h after induction), prevented the cognitive impairments that are typically induced by pneumococcal meningitis (Barichello et al., 2009). Another significant factor is the ability of an antimicrobial agent to penetrate into the BBB and CNS (Honda & Warren, 2009). New targets are being investigated for adjunctive therapy in meningitis. In a rat model, exogenous administration of the intracerebroventricular BDNF was found to block caspase-3 and reduce neuronal apoptosis in pneumococcal meningitis and reduce cortical necrosis in meningitis caused by *Streptococcus agalactiae* (Bifrare et al., 2005). In another study with the rat model of bacterial meningitis, administration of exogenous BDNF protected and increased the neuronal cell population from inflammatory brain injury (Li et al., 2005, 2007). Furthermore, decreased hippocampal BDNF levels were correlated with memory impairment in adult rats that were infected with pneumococcal and *Streptococcus agalactiae* meningitis in the neonatal period (Barichello et al., 2010, 2013).

Dexamethasone is an anti-inflammatory drug with the ability to suppress inhibitor of κB (IκB) degradation (Bhattacharyya et al., 2010), which decreases pro-inflammatory cytokines and inhibits the reactive oxygen species produced by leukocytes (Dandona et al., 1999). Dexamethasone aggravated hippocampal apoptosis and learning deficiency in rat pups infected with *Streptococcus pneumoniae* by intracisternal injection on postnatal day 11 (Leib et al., 2003) and increased hippocampal neuronal apoptosis in a rabbit model of *E. coli* meningitis (Spreer et al., 2006). In a human study, 52 full-term neonates with bacterial meningitis were alternately assigned to receive or not receive dexamethasone; both groups showed a similar clinical response and similar frequencies of mortality and sequelae (Daoud et al., 1999). On the other hand,
The use of non-bacteriolytic antibiotics has been shown to be potentially beneficial in the treatment of bacterial meningitis in infants. In a rat model of pneumococcal meningitis, daptomycin was more efficient than ceftriaxone in decreasing the bacterial titre after infection, and only the animals treated with ceftriaxone showed cortical damage (Grandgirard et al., 2007). In a rat model of Streptococcus agalactiae meningitis, animals treated with a monoclonal antibody against TNF-α had less hippocampal injury than controls (Bogdan et al., 1997). One strategy with which to prevent brain damage is to restrict leukocyte recruitment to the CSF. Fucoidin is a polysaccharide that blocks the leukocyte receptor L-selectin. Intravenous treatment of rats with fucoidin at 0, 2, 4 and 6 h after pneumococcal meningitis induction reduced intracranial pressure and pleocytosis in the CSF (Angstwurm et al., 1995). Furthermore, fucoidin injected intracisternally inhibited the accumulation of CSF leukocytes upon the administration of antibiotics in experimental meningitis (Granert et al., 1998).

Reactive oxygen species are produced by resident immune cells in the brain and by leukocyte recruitment, as part of the host’s reaction to invasive bacterial infection. To inhibit the production of oxidative stress, the use of the N-acetylcysteine and deferoxamine as adjuvant treatment prevented cognitive impairment in animals submitted to pneumococcal meningitis (Barichello et al., 2012b). In another study, infant rats treated with antioxidant drugs, including N-acetylcysteine, deferoxamine and trylizadmesylate, showed reduced cortical injury and mortality (Auer et al., 2000).

Conclusion

Despite important advances in treatment, neonatal meningitis is one of the most significant infectious diseases of the CNS, with high mortality and morbidity. Experimental animal models, despite limitations, provide an understanding of the complex pathophysiology of this disease and suggest new adjunctive therapies.

Acknowledgements

This research was supported by grants from CNPq, FAPESP, FAPEMIG, UNESCO, INCT-TM and the L’Oréal-UNESCO Brazil Fellowship for Women in Science 2011. The authors declare that they have no conflicts of interest.

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