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REVIEW

Molecular epidemiology of *Escherichia coli* causing neonatal meningitis

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Abstract

Escherichia coli is the second cause of neonatal meningitis which is a major cause of neonatal mortality and is associated with a high incidence of neurological sequelae. *E. coli* neonatal meningitis (ECNM) strains, as other extra-intestinal pathogenic *E. coli*, mainly belong to the phylogenetic group B2 and to a lesser extent to group D, but are distributed in fewer clonal groups. One of these, the O18:K1:H7 clone is worldwide distributed meanwhile others such as O83:K1 and O45:K1 are restricted to some countries. Over the past few years, major progress has been made in the understanding of the pathophysiology of *E. coli* O18:K1:H7 neonatal meningitis. In particular, specific virulence factors have been identified and are known to be carried by ectochromosomal DNA in most cases. Molecular epidemiological studies, including characterization of virulence genotypes and phylogenetic analysis are important to lead to a comprehensive picture of the origins and spread of virulence factors within the population of ECNM strains. To date, all the known genetic determinants obtained in ECNM strains are not sufficient to explain their virulence in their globality and further studies on clonal groups different from the archetypal O18:K1:H7 clone are needed. These studies would serve to find common pathogenic mechanisms among different ECNM clonal groups that may be used as potential target for a worldwide efficacious prevention strategy.

Keywords: *Escherichia coli*; Neonatal meningitis; Phylogenetic group; Virulence factors; Pathogenicity islands

Contents

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Introduction

Escherichia coli has the unique feature to be both, the major species of the nonanaerobic intestinal commensal flora of most humans, as well as the major community-acquired and nosocomial pathogen causing various infections including diarrhoea, urinary tract infections, sepsis, and neonatal meningitis. Despite many advances have been made in diagnostics, therapeutics and supportive care of neonatal infections, *E. coli* neonatal meningitis (ECNM) has still a high rate of morbidity and mortality. Although several specific bacterial factors have been identified, the ability of *E. coli* to colonize, disseminate and invade the subarachnoidal space is not fully understood. Complete understanding of the pathogenesis of *E. coli* causing neonatal meningitis would lead to the development of novel strategies to prevent *E. coli* meningitis.

Epidemiology of neonatal meningitis

Global incidence of neonatal meningitis

The World Health Organization lists meningitis among the five leading neonatal infections worldwide. Each year, in developing countries, about 50,000 newborns die of meningitis (mortality rate 40%), representing about 1% of all causes of neonatal mortality (Stoll, 1997). In industrialized countries the incidence of neonatal bacterial meningitis was about 1 per 1000 live births until the 1980s (Bell et al., 1989; Franco et al., 1992). The incidence has now fallen to between 0.22 and 0.37 per 1000 live births (de Louvois, 1994; de Louvois et al., 1991; Fortnum and Davis, 1993; Hristeva et al., 1993; Overall, 1970), with a mortality rate of 20–30% (de Louvois et al., 1991; Hristeva et al., 1993).

Neonatal meningitis: The main bacterial pathogens

E. coli is currently the second cause of neonatal meningitis, behind group B streptococci (GBS) and on average, there is one case due to *E. coli* for two cases due to GBS. Actually, GBS and *E. coli* account for between 70% and 80% of cases of neonatal bacterial meningitis in industrialized countries (May et al., 2005). In developing countries GBS meningitis is far less frequent than forms due to *Enterobacteriaceae* (Stoll, 1997). Certain *Enterobacteriaceae*, such as *Proteus mirabilis* and *Citrobacter diversus*, rarely cause neonatal meningitis but are frequently isolated from brain abscesses (Unhanand et al., 1993).

Epidemiological and clinical characteristics of *E. coli* meningitis

Mulder et al. (1984) and de Louvois et al. (1991) reported ECNM incidence rates of, respectively, 0.12 and 0.06 per 1000 live births. No other large studies published since the 1980s have examined the incidence of ECNM. However, by crossing global meningitis incidence data (de Louvois, 1994; Fortnum and Davis, 1993; Hristeva et al., 1993) with the results of bacteriological epidemiological studies, the incidence of *E. coli* meningitis in industrialized countries seems to be stabilized to 0.1/1000 live births. Most cases of *E. coli* meningitis occur during the first months of life; exceptional adult cases are associated with certain underlying conditions, such as neurosurgery and trauma. The vast majority of these infections occur in the neonatal period (<28 days), while about 10% occur between 1 and 3 months of age (Unhanand et al., 1993). Median age of onset is between 6 and 9 days (Dellagrammaticas et al., 2000; Mulder et al., 1984; Unhanand et al., 1993). Few risk factors for ECNM have been identified. Nearly one-third of cases involve premature infants (Dellagrammaticas et al., 2000; Mulder et al., 1984) and *E. coli* is the leading cause of neonatal meningitis in this group of patients. Urinary tract infection may be present in 20% of cases (Unhanand et al., 1993). Overall, the mortality rate ranges from 20 to 29% (de Louvois et al., 1991; Franco et al., 1992; Mulder et al., 1984; Unhanand et al., 1993), but it rises to nearly 40% in premature infants (Unhanand et al., 1993). Nearly half the victims of ECNM develop neurological sequelae, which are more frequent when the meningitis is complicated by ventriculitis (10%) (Dellagrammaticas et al., 2000; Mulder et al., 1984; Unhanand et al., 1993) or intracerebral abscess (<3%) (Dellagrammaticas et al., 2000; Unhanand et al., 1993).

Pathophysiology of *E. coli* neonatal meningitis

In most cases the sequence of events leading to meningitis is as follows. Following acquisition from the mother's flora or from environment *E. coli* colonizes the infant intestinal tract. Then the development of ECNM comprises three main pathophysiological steps. The first