Review

Group B streptococcus infection and diabetes: A review

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Streptococcus agalactiae, a group B streptococcus (GBS), has been considered to be a major pathogen in neonates and pregnant women. Recently, there is accumulating concern about its significance for pathogenesis in non-pregnant adult patients. Diabetes is one of the most important underlying diseases for the development of GBS infection. This review will focus on the risk factors and clinical manifestations of GBS infections, and also introduce two patients with hyperglycemic hyperosmolar syndrome and diabetic ketosis who were complicated with pneumonia due to GBS.

Key words: Diabetic ketosis, group B streptococcus (GBS), hyperglycemic hyperosmolar syndrome, pneumonia.

INTRODUCTION

Streptococcus agalactiae, a group B streptococcus (GBS), is the leading cause of sepsis and meningitis in newborn infants (Schuchat et al., 1990). GBS infections cause substantial pregnancy-related morbidity (Dillon et al., 1987). Until recently, it was believed that GBS infections in the rest of the population were very rare. However, GBS infections may also be an emerging public health problem in non-pregnant adult patients (Schwartz et al., 1991; Farley et al., 1993; Jackson et al., 1995). GBS infection has been reported to occur exclusively in adults with serious underlying conditions (Schwartz et al., 1991; Farley et al., 1993; Jackson et al., 1995). Diabetes is one of the most important underlying diseases for the development of GBS infections (Schwartz et al., 1991; Farley et al., 1993; Jackson et al., 1995; Colford et al., 1995; Muñoz et al., 1997; Larppanichpoonphol et al., 2001; Tee et al., 2002; Matsubara et al., 2009; Georgieva et al., 2010; Lamberts et al., 2010; Skoff et al., 2009; Schuchat et al., 1990). This review will highlight the risk factors including the underlying diseases, and clinical manifestations of GBS infections, and introduce two patients with diabetic emergency such as hyperglycemic hyperosmolar syndrome and diabetic ketosis, who were complicated with pneumonia due to GBS.

RISK FACTORS FOR GBS INFECTION

Schwartz et al. (1991) reported the invasive diseases due to GBS of adults in a population–based assessment which was performed in metropolitan Atlanta during 1982 and 1983; compared with the general population’s risk of infection, the risk in patients with diabetes and cancer was significantly increased (Schwartz et al., 1991) (Table 1). In another study, performed in metropolitan Atlanta between 1989 and 1990, the risk was high in older patients with diabetes and cancer (Farley et al., 1993) (Table 1). HIV infection was also associated with an age-specific risk for GBS infection. The study suggested that GBS infection was a major health problem not only in pregnant women but also in non-pregnant adults, especially the elderly, and patients with chronic diseases. In a study performed in 3 metropolitan areas in the United States between 1991 and 1992, liver cirrhosis, diabetes, breast cancer, decubitus ulcer, and neurogenic bladder

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were significantly associated with an increased risk for community-acquired GBS infections after controlling for age in multivariate analysis (Jackson et al., 1995) (Table 1).

In a retrospective study of 32 adult patients with GBS bacteremia in U.S.A., non-hematologic cancer was the most frequently associated condition (25%), 19% of the patients had diabetes (Colford et al., 1995). In analysis of 90 patients with GBS bacteremia in Spain (between 1985 and 1994), the most common underlying conditions were liver diseases (35.3%), malignancies (33.3%), and diabetes (27.5%) (Muñoz et al., 1997). In an analysis of 36 episode of GBS bacteremia in U.S.A. (between 1980 and 1984), most common underlying disease was diabetes (49%) (Larppanichpoonphol et al., 2001). In an analysis of 85 patients with GBS bacteremia in Singapore (between 1996 and 1998), co-morbidity included malignancies in 28.8% of patients, diabetes in 11.5% and liver disease in 9.6% (Tee et al., 2002). In a retrospective review of patients (6 infants and 52 adults) with invasive GBS infections in Japan (between 1998 and 2007), most frequent underlying condition was diabetes, with majority (18/23) of such patients showing poor blood glucose control with HbA1c > 8.0% (Matsubara et al., 2009). In an analysis of 27 patients with GBS-infected infective endocarditis in Spain (between 1984 and 2008), the most frequent underlying diseases were diabetes (25.9%), chronic obstructive pulmonary disease (14.8%), neoplasms (14.8%), urogenital disorders (11%) and chronic liver disease (11%) (Georgieva et al., 2010). In an analysis of invasive GBS infections in adults in Denmark (between 1999 and 2004), diabetes was observed in 15% of cases, 12% had alcohol abuse and 7% had cancer (Lambertsen et al., 2010). In an analysis of 19,512 patients with invasive GBS diseases in U.S.A. (between 1990 and 2007), diabetes was present in 44.4% of cases (Skoff et al., 2009). Taking the results of these three population-based studies (Table 1) and other 9 studies (Table 2) together, it could be concluded that liver diseases, cancer and diabetes are common underlying diseases in non-pregnant adults with GBS infections, and that diabetes is one of the most important underlying medical conditions for the development of GBS infections.

**TABLE 1. Risk factors for group B. streptococcus infection.**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Risk factor</th>
<th>Relative risk/ odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al.</td>
<td>Diabetes</td>
<td>10.5 (95% CI, 7.8 - 14.4)</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td>16.4 (95% CI, 11.5 - 23.3)</td>
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<tr>
<td></td>
<td>Liver cirrhosis</td>
<td>9.7 (95% CI, 3.5 - 26.9)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>3.0 (95% CI, 1.9 - 4.7)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>3.5 (95% CI, 1.9 - 6.4)</td>
</tr>
<tr>
<td></td>
<td>Breast cancer</td>
<td></td>
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<tr>
<td></td>
<td>Decubitus ulcer</td>
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<td></td>
<td>Neurogenic bladder</td>
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<tr>
<td>Farley et al.</td>
<td>Diabetes (20 - 44 aged patients)</td>
<td>30 (95% CI, 11 - 79)</td>
</tr>
<tr>
<td></td>
<td>Cancer (20 - 49 aged patients)</td>
<td>4.0 (95% CI, 12 - 67)</td>
</tr>
<tr>
<td></td>
<td>HIV infection (30 - 49 aged patients)</td>
<td>16.4 (95% CI, 11 - 78)</td>
</tr>
</tbody>
</table>

Cl (confidence interval), HIV (human immunodeficiency virus).

**CLINICAL DIAGNOSES OF GBS INFECTION IN DIABETIC PATIENTS**

The most common clinical diagnosis of GBS infection are skin, soft tissue, and bone infection, and such infections occurred in 36% of the patients (Farley et al., 1993). 56% of patients with skin, soft tissue, and bone infection were diabetic. 5% of the patients (all patients with diabetes) had osteomyelitis complicated with foot ulcer. Bacteremia with non-identified infection source was the next common clinical diagnosis (30%). Other common clinical diagnoses included urosepsis (14%), pneumonia (9.5%), and peritonitis (7.3%). Shown in Table 3, diabetic patients with GBS infection have been reported to show various clinical manifestations. GBS infection induce skin and soft tissue infections such as diabetic foot infection (Petersen et al., 2010), necrotizing fasciitis (Lee et al., 2008), multiple loculated shoulder abscess (Varughese et al., 2008), scrotal subcutaneous abscess (Takemura et al., 2010) and pyomyositis (Walling et al., 1991) in diabetic patients. GBS causes respiratory infections such as retropharyngeal phlegmon (Sapunar et al., 2008), lung abscess (Obase et al., 1997), subphrenic abscess (Kawasaki et al., 1985), and empyema (George et al., 1987), and also causes urological infections in diabetic patients (Turan et al., 2008; Amisano et al., 1994). Systemic GBS infections in diabetic patients such as post-splenectomy sepsis (Fish et al., 1985), bacteremia (Colford et al., 1995), infective
endocarditis (Ivanova et al., 2010) have been reported. GBS is very invasive for diabetic adult patients, GBS induce endogenous endophthalmitis (Lee et al., 2002) and meningitis (Farley et al., 1993).

In a population-based assessment of invasive GBS infections in non-pregnant adults, GBS was cultured from the blood in 94% of patients (Farley et al., 1993). GBS was also cultured from urine (13%), soft tissue or bone (8.6%), peritoneal fluid (5%), pleural fluid or sputum (2.9%), cerebral fluid (2.9%), and synovial fluid (1.4%). These data suggest that GBS is likely to induce bacteremia and also invade every parts of body (Farley et al., 1993).

**GBS INFECTION AND DIABETIC EMERGENCY**

We will introduce patients with diabetic emergency (hyperglycemic hyperosmolar syndrome and diabetic ketosis) complicated with GBS infection. A 77-year-old man developed dyspnea in December, 2010, and he was diagnosed as having bronchial asthma and was treated by steroid in January, 2011. He was referred and admitted to our hospital due to disturbed consciousness. On admission, his blood glucose (651 mg/dl) and HbA1c (8.2 %) levels significantly increased. Serum levels of blood urea nitrogen (BUN) (80 mg/dl; normal range, 8 to 22 mg/dl), creatinine (Cr) (2.33 mg/dl; reference range, 0.4 to 0.7 mg/dl) and C-reactive protein (CRP) (4.69 mg/dl; reference range, 0 to 0.3 mg/dl) were remarkably elevated. Urinalysis revealed no ketone bodies. These symptoms and data suggested the presence of hyperglycemic hyperosmolar syndrome. The computed tomography (CT) of the chest showed pleural effusion and consolidation in bilateral lung, suggesting the presence
of pneumonia (Figure 1a). Culture of sputum grew GBS, which was sensitive to antibiotics except for levofloxacin, minocycline and erythromycin. His blood glucose levels were promptly decreased by the intensive insulin therapy and CRP level decreased to 1.71 mg/dl by antibiotics (sulbactam/ampicillin 3g /day) within a week.

A 54-year-old man was admitted to the emergency room in our hospital due to disturbed consciousness. On admission, his blood glucose (1,288 mg/dl) and HbA1c (14.4%) levels significantly increased. Serum levels of BUN (49 mg/dl; normal range, 8 - 22 mg/dl), Cr (1.13 mg/dl; normal range, 0.4 to 0.7 mg/dl) and CRP (22.6 mg/dl; normal range, 0 to 0.3 mg/dl) were also elevated. Blood tests revealed significantly elevated serum total ketone bodies (5.162 µmol/L; normal, < 130 µmol/L) and normal pH (pH = 7.352), suggesting the development of diabetic ketosis. The CT of the chest showed centrilobular nodular and branching opacities and focal areas of consolidation, suggesting the presence of bronchopneumonia (Figure 1b). Culture of sputum yielded GBS and Staphylococcus aureus; GBS was sensitive to almost antibiotics without levofloxacin. His blood glucose levels were promptly decreased by the intensive insulin therapy and CRP level decreased to 1.54 mg/dl by antibiotics (tazobactam/piperacillin 18 g /day) in two weeks.

Mazade et al. (2001) hypothesized that severe hyperglycemia would alter neutrophil metabolism by diverting NADPH from superoxide production into the aldose reductase-dependent polyol pathway that converts glucose into sorbitol and thus would impair opsonophagocytosis of GBS, and studied the effect of hyperglycemia on neutrophil-mediated phagocytosis of GBS. They found that neutrophils from type 2 diabetic adults had no intrinsic phagocytic defect under baseline glycemic conditions. After equilibration in 60 or 120 mM glucose, opsonophagocytosis activity was significantly reduced, and neutrophil superoxide production was also significantly reduced by hyperglycemia. An aldose reductase inhibitor increased superoxide production and significantly improved opsonophagocytosis of GBS, suggesting that diversion of NADPH into the polyol pathway is one mechanism by which opsonophagocytosis of GBS is impaired during hyperglycemia. In a retrospective study of patients with GBS infections in Japan, invasive GBS infection was significantly associated with poor blood glucose control with HbA1c > 8.0% (Matsubara et al., 2009), supporting the importance of hyperglycemia for susceptibility to GBS infections. Our patients with severe hyperglycemia might be susceptible to GBS infections. Aspiration pneumonitis is a life-threatening complication of diabetic ketosis and hyperglycemic hyperosmolar syndrome, and gastroparesis including gastric dilatation and vomiting have been considered to make aspiration of gastric contents in comatose diabetic patients (Silversides et al. 2009). Our patients had disturbed consciousness on the admission; aspiration might induce the onset of pneumonia, and hyperglycemia might induce the development of GBS infection.
To our knowledge, the association of GBS infections to diabetic emergency such as hyperglycemic hyperosmolar syndrome and diabetic ketoacidosis has never been reported. To save patients with diabetic emergency, it is very important to control infections. We should think of GBS infection when we treat patients with hyperglycemic hyperosmolar syndrome and diabetic ketoacidosis.

CONCLUSION

Diabetes may be one of the most important risk factor for the development of GBS infection. GBS is likely to induce bacteremia and also invade every part of body, therefore, diabetic patients with GBS infection may show various clinical manifestations. GBS infection may be also associated with diabetic emergency such as hyperglycemic hyperosmolar syndrome and diabetic ketoacidosis.

REFERENCES


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