Rapid Emergence of emm84 among Invasive Streptococcus pyogenes Infections in Finland

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From 2005 to 2007, in Finland, the incidence of invasive Streptococcus pyogenes disease increased sharply, partly due to the uncommon emm84 gene becoming more prevalent from 2006 onwards. The overall case fatality rate of infections caused by strains carrying emm84 was not significantly different than that of infections caused by other types (7% versus 10%, respectively; P = 0.50).

The incidence of Streptococcus pyogenes (group A streptococcus [GAS]) disease has been shown to vary over time and geographic region (8, 12, 20, 31), possibly reflecting the population’s susceptibility to particular strains but also variation in the predominant emm types (19). Given the differential pathogenic potential of emm types (1, 27), this may result in fluctuations in the severity of invasive GAS (iGAS) disease.

In 2006, Finnish clinicians started reporting severe manifestations of iGAS disease in previously healthy patients, with rapidly proceeding infections leading to poor outcome. At the same time, the new and uncommon emm84 gene emerged and rapidly became more common. These events prompted an investigation of geographic, patient, and outcome information for emm84 and other iGAS cases and molecular properties of emm84 isolates in more detail.

Surveillance of iGAS disease in Finland (population, 5.3 million) is carried out by clinical microbiology laboratories reporting the isolation of S. pyogenes from blood and cerebrospinal fluid to the National Infectious Disease Register at the National Public Health Institute. The corresponding GAS isolates are submitted to the national reference laboratory for typing. In this study, iGAS notifications and isolates from January 2005 to December 2007 were included and matched for emm typing. In this study, iGAS notifications and isolates from January 2005 to December 2007 were included and matched for case ascertainment. Patients’ vital statuses at 7 days of positive blood or cerebrospinal fluid culture were obtained from the Population Information System.

(These results have been partly presented at the European Scientific Conference on Applied Infectious Disease Epidemiology, Stockholm, Sweden, October 2007 [23a] and at the XVII Lancefield International Symposium on Streptococci and Streptococcal Diseases, Porto Heli, Greece, June 2008 [23b].)

Isolates were tested for sensitivity to bacitracin, and the group antigen was identified using a Streptex test (Remel Europe Ltd., United Kingdom). emm typing was performed for all isolates according to guidelines provided by Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/biotech/strep/strepblast.htm) as previously described (23). Susceptibility to levofloxacin, erythromycin, clindamycin, and tetracycline was determined by an agar dilution method. Interpretations of MIC results were done according to criteria for Streptococcus spp. other than S. pneumoniae as recommended by the Clinical and Laboratory Standards Institute (2). Pulsed-field gel electrophoresis (PFGE) was performed for emm84 isolates using standard methods (23, 25), analyzed using BioNumerics (version 4.6; Applied Maths, Belgium), and interpreted according to general guidelines (29). Strains with ≥80% similarity were considered to be related types. All isolates from 2005 to 2006 and five selected emm84 isolates of different PFGE strain types isolated in 2007 were T serotyped (17, 24). Superantigen (SAg) profiling was performed for 10 selected emm84 isolates including different PFGE strain types in two multiplex PCRs for the detection of the streptococcal superantigen ssa gene and the pyrogenic exotoxin genes speA, speB, speC, speF, speG, speH, and speJ, and a single PCR was used to detect the streptococcal mitogenic exotoxin smeZ gene (4, 22). Medical records of patients with infections with emm84 isolates clustered by time within one hospital were reviewed to identify underlying conditions and any common exposure or contacts between the patients. Data were analyzed and compared using Fisher’s exact, χ2, and Kruskal-Wallis tests, where appropriate, with Intercooled Stata 9.1 for Windows (StataCorp) and GraphPad software (http://www.graphpad.com/quickcalcs/index.cfm).

From January 2005 to December 2007, 479 persons with iGAS infections were identified in Finland (annual incidence of 2.1, 3.1, and 3.9 cases per 100,000 people in 2005, 2006, and 2007, respectively). For 474 notifications, a corresponding isolate was received. A total of 37 emm types were represented, most commonly emm1 (19%), emm28 (17%), emm84 (12%), emm75 (7%), and emm89 (6%).

emm84 (emm84.0) strains emerged in November 2005 and rapidly became more prevalent (Fig. 1), constituting 15% (24/161) of isolates in 2006 and 16% (32/203) of isolates in 2007,
with a significant increase from 2005 (1/110 isolates; \( P < 0.001 \)). Infections with \( \text{emm84} \) strains localized to 10 of 20 health care districts in the southern part of the country, primarily in the largest health care district (Helsinki metropolitan area [population, 1.4 million]), where \( \text{emm84} \) originally emerged and where 70% of infections caused by \( \text{emm84} \) strains occurred. In this district, \( \text{emm84} \) was the most common type in 2006 (29%) and 2007 (26%), compared to 4% and 10% in all other districts combined, respectively.

\( \text{T} \) serotyping of \( \text{emm84} \) isolates resulted in a variety of type combinations: NT (13 isolates), T11 (nine isolates), T11/B3264 (two isolates), T1 (two isolates), T3 (two isolates), T3/B3264 (one isolate), and T8/25/imp19 (one isolate) (9). PFGE analysis revealed one predominating strain type (A1) among \( \text{emm84} \) strains until 2007, when sporadic cases with five more strain types emerged (Fig. 2). Variability in SAg gene profiles existed among \( \text{emm84} \) isolates, but related PFGE strain types had similar SAg profiles. The \( \text{speB} \), \( \text{speF} \), and \( \text{speG} \) genes were detected in all strain types, while the presence of \( \text{smeZ} \) and \( \text{speJ} \) varied. \( \text{speA} \) and \( \text{smeZ} \) were found in two related strain types, B1 and B2 (both with unusual serotype T1), one of which caused a fatal infection. These results were in line with data from other studies reporting the existence of the \( \text{speB} \), \( \text{speF} \), and \( \text{speG} \) genes in the majority of isolates (4, 6, 14). A Swedish study described the SAg profile of an \( \text{emm84} \) strain harboring \( \text{speG} \), \( \text{speH} \), and \( \text{speJ} \) but lacking the \( \text{speA} \) and \( \text{smeZ} \) genes and thus being of a different clonal origin (15). Single \( \text{emm} \) type seems to have a wide genotypic diversity in SAg content, especially for the prophage-associated genes (15). Strains harboring \( \text{speA} \) and/or \( \text{smeZ} \) genes are potentially involved in severe disease, but the correlation between invasiveness and the presence of single SAg genes has not been proven (4, 7, 15, 18, 26).

\( \text{emm84} \) isolates were sensitive to levofloxacin, erythromycin, and clindamycin, and 2% (1/57) of the isolates were resistant to tetracycline. The overall erythromycin resistance during 2005 to 2007 was <2% (8/474 isolates); this was expected, as the rate has declined since 1998 (Finnish Study Group for Antimicrobial Resistance [http://www.ktl.fi/portal/english/projects/fire/finres/]). Similarly low resistance rates were previously reported in Denmark (14) and the United States (21).

Patients with infection caused by an \( \text{emm84} \) strain were older than patients infected by other types (median, 58 versus 53 years; \( P < 0.05 \)). None of the patients with infection caused by an \( \text{emm84} \) strain were under 30 years of age; 58% were males, compared to 54% with other \( \text{emm} \) types.

The overall case fatality rate from 2005 to 2007 in patients infected with \( \text{emm84} \) strains was 7%, which was not significantly different than that of infections caused by other types (10%; \( P = 0.50 \)). The severe disease manifestations reported by clinicians were more likely explained by other prevalent \( \text{emm} \) types at the time. The overall case fatality rate of iGAS disease in Finland (9%) was generally low in comparison to rates reported for other European countries and the United States (4, 6, 13, 20).

Within the Helsinki metropolitan area health care district in 2006, infections caused by \( \text{emm84} \) strains were treated in seven hospitals, one of which had a cluster of cases from April to October involving seven patients (six males and one female; age range, 30 to 87 years). All isolates fell into PFGE strain type A1 but had variable \( \text{T} \) serotypes (T11, NT, and T3). No common exposure or contacts could be found for these patients. Their medical records revealed that all of them had one or more predisposing factors for infection: traumatic wound (six patients), diabetes (four patients), intravenous drug use (two patients), alcoholism (two patients), immunodeficiency (two patients), and malignancy (one patient). None had a fatal outcome.

\( \text{emm84} \) is not a common type. A study from Greece reported a high prevalence of serotype M84 in erythromycin-resistant...
GAS strains causing noninvasive infections in children from 1997 to 1998 (32). At the same time in the United Kingdom, M84 emerged as a predominant type and disappeared soon after (5). A recent publication from Hungary described two erythromycin- and clindamycin-sensitive emm84 isolates among invasive infections with fatal outcome (11). Apart from these findings, sporadic infections by emm84 with variability in macrolide resistance have been reported (15, 21, 28, 30).

Our findings are limited in some respects. Firstly, although emm84 was first detected in Finland in 2005, we cannot be certain that this type was not present before. We have emm typing data for all isolates from 2004 and for a majority of isolates from 2003, and emm84 was not detected among these isolates. T typing, which was the primary typing method until 2003, is nonspecific for this strain type and would have failed to characterize it. Secondly, our clinical information on emm84 and other cases is limited; however, a putative cluster of these cases was investigated in more detail.

In conclusion, our study demonstrates a rapid change in genotype prevalence and its impact on the rate of iGAS infections, the increase of which was partly due to the emergence of emm84 strains. The sudden upsurge of infections caused by emm84 strains presumably reflects the population’s lack of immunity against this uncommon strain type. Type Memm84 is not included in the 26-valent or hexavalent M-protein-based vaccine approaches, which may need to be reevaluated and adapted to future changes in type prevalence to ensure the efficacy of the vaccine (3, 10, 16, 19). Our findings further emphasize the importance of global emm type surveillance and outcome analyses.

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