



## Case Report

## Familial segregation of group B streptococcal infection in a consanguineous kindred



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## SUMMARY

Two cases of neonatal group B streptococcal (GBS) infection occurring in a large consanguineous kindred are described. The observation suggests that susceptibility to isolated GBS disease in this family may have been the result of an inborn error of immunity inherited as a Mendelian autosomal recessive trait.

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### 1. Introduction

Group B *Streptococcus* (GBS) is a common colonizer of the human gastrointestinal and genitourinary tracts causing disease primarily in pregnant/post-partum women and infants younger than 3 months of age.<sup>1</sup> The estimated global incidence of neonatal GBS disease (defined as GBS infection occurring at 0–89 days of life) is 0.53 per 1000 live births (see additional references in the **Supplementary Material**).

Neonatal GBS disease is commonly considered an environmental condition, linked to the virulence of the microorganism or to ‘neonatal immunodeficiency’. However, after the acquisition of GBS from the maternal genital tract, breast milk, or the environment, most infants are colonized by GBS without developing an overt infection, and only a small proportion of exposed infants develop

early-onset disease (EOD; onset at ≤6 days of life) or late-onset disease (LOD; onset at >6 days of life). Only 1–2% of infants colonized at birth develop EOD (10–30% of all pregnant women are colonized with GBS, and approximately 50% of infants born to colonized mothers are in turn colonized with GBS).<sup>1</sup> The proportion of colonized infants that develop LOD is probably lower, given the decreasing incidence with age and a likely increasing cumulative exposure/colonization rate with increasing age.

Known risk factors (reported in the **Supplementary Material**) identify groups of infants at risk of invasive infection,<sup>1</sup> but are unable to predict the occurrence of GBS disease at the individual level. Furthermore, a significant proportion of GBS infection occurs in otherwise healthy full-term infants in the absence of established risk factors,<sup>2</sup> suggesting a role for additional, as-yet unidentified individual mechanisms of susceptibility.

Anecdotal reports in the literature describe the occurrence of GBS disease in association with primary or acquired immunodeficiencies (reviewed in the **Supplementary Material**). Invasive GBS infection has also been reported in infants with interleukin

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1 receptor-associated kinase 4 (IRAK-4) and myeloid differentiation primary response 88 (MyD88) deficiency,<sup>3,4</sup> two conditions causing vulnerability to a broad range of pyogenic bacteria, suggesting that toll-like receptor/interleukin 1 receptor signalling is essential for the protective responses to GBS. However, GBS infection is a rare manifestation of IRAK-4/MyD88 deficiency and almost always occurs as a sporadic and isolated infection. Thus, there is so far no clear evidence for a host genetic contribution to susceptibility to isolated GBS disease.

This is the first description of two cases of isolated neonatal GBS disease occurring in two infants in two related families in a large consanguineous kindred of the Sinti ethnic group. The report provides the first clue of a possible genetic origin of isolated GBS disease.

## 2. Case reports

The pedigree of the large consanguineous kindred is shown in Figure 1. No known immunological diseases, immunodeficiencies, or autoimmune diseases were reported in the family. No life-threatening infections, including GBS disease, were reported other than those occurring in case 1 (V.4) and case 2 (V.5). The 3-year-old sister of case 1 and the three sisters of case 2 are healthy.

Case 1 was a 48-day-old boy admitted to the paediatric unit of the hospital because of clinical signs of sepsis. Two blood cultures were positive for GBS. The infant was initially treated with a 26-day antibiotic course and with subsequent additional antibiotic courses due to relapsing fever, increases in inflammatory markers, seizures, and the discovery of an intracranial subdural empyema (**Supplementary Material**, Figure S1). The clinical course was eventually favourable. Antibiotics were stopped and the infant was discharged home. He is currently aged 1 year and 3 months and is free of infection. A detailed history of the clinical course and the laboratory tests performed during his hospital stay are reported in the **Supplementary Material** (Table S1). The baseline immunological evaluation including lymphocyte subpopulation numbers,

immunophenotype, and serum immunoglobulins was normal for the patient's age (**Supplementary Material**, Table S2). A flow cytometry-based evaluation of the cleavage of membrane-bound L-selectin (CD62L) on granulocytes upon activation with lipopolysaccharide, to assess the integrity of the signalling from the toll-like receptors, was performed.<sup>5</sup> Despite a low baseline expression of CD62L in the patient, a shedding response could be observed, thus excluding a complete IRAK-4 or MyD88 deficiency (**Supplementary Material**, Figure S2).

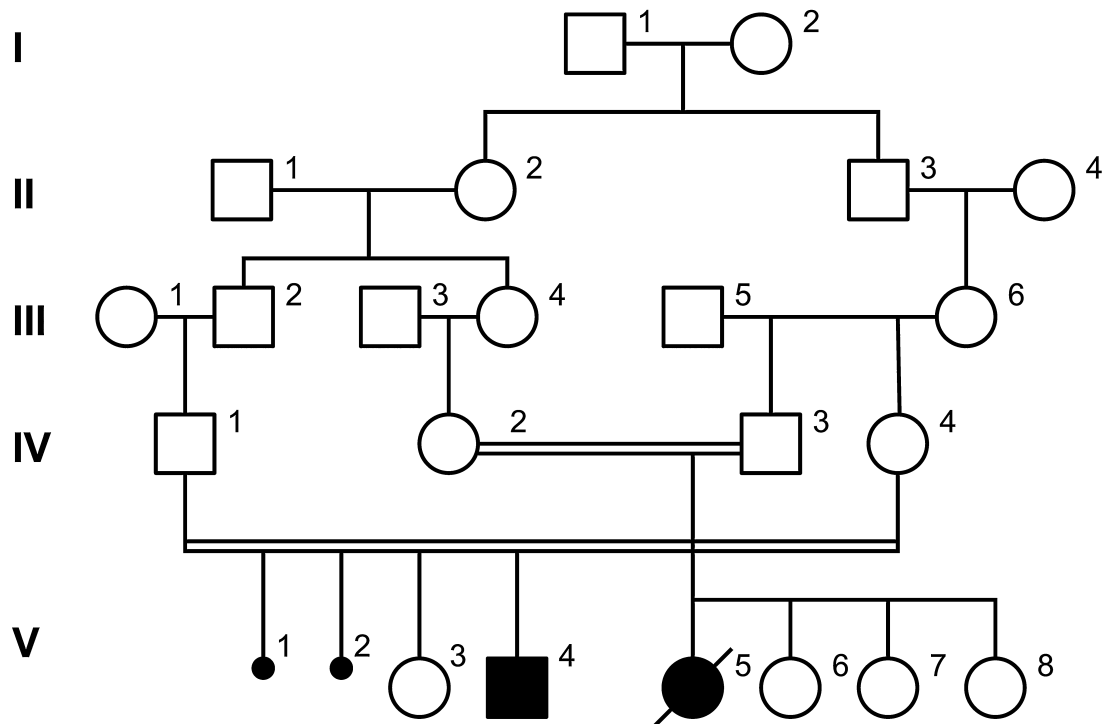
Case 2 was a girl born at another hospital to a 32-year-old primigravida by spontaneous delivery at 35 weeks of gestation. The birth weight was 2170 g. The maternal vaginal–rectal swab was not performed because of the premature delivery. The infant was immediately transferred to the neonatal intensive care unit due to her poor clinical condition. Despite antibiotics, mechanical ventilation, and cardio-circulatory support, the infant died at 48 h of life. GBS was isolated from blood culture.

## 3. Discussion

To our knowledge, this is the first report of familial recurrence of isolated GBS infection in a large consanguineous kindred.

Each of the two reported cases, taken separately, clinically overlaps with previous reports of sporadic GBS disease in its classical early-onset (case 2) and late-onset (case 1) presentations. Case 1 was a healthy full-term infant who was discharged home and who developed GBS disease in the absence of any known risk factor. Similar cases are commonly seen among patients admitted to neonatal intensive care or paediatric units. The limited information available for case 2 suggests a typical presentation of fulminant early-onset GBS disease, which can occur with or without established risk factors.

Despite the classical presentations, the cases drew attention because of the familial recurrence in the presence of consanguinity, suggesting a shared common determinant of susceptibility by



**Figure 1.** The large consanguineous kindred. The parents of case 1 (V.4) are second-degree cousins. The parents of case 2 (V.5) are second-degree cousins. A high degree of consanguinity is expected, since inbreeding is common in Sinti communities.

affected but not unaffected individuals, both exposed to the same environment.

Complete IRAK-4 and MyD88 deficiencies were excluded by a simple flow cytometry assay (**Supplementary Material**, Figure S2).<sup>5</sup> Indeed, despite low baseline CD62L expression on the neutrophil surface, the shedding of CD62L could still be observed after stimulation with lipopolysaccharide.

Low maternal serum anti-capsular GBS antibodies have been associated with an increased risk of GBS disease early in life. Serum maternal anti-GBS antibody levels were not measured; thus, it cannot be excluded that fluctuations in their concentrations may explain the susceptibility in cases 1 and 2 and resistance in their non-affected siblings. However, the consanguinity of the family makes more likely the hypothesis that the determinant of susceptibility is a Mendelian defect inherited with an autosomal recessive pattern, underlying a rare inborn error of immunity affecting the protective primary innate immune response to GBS. GBS disease occurred in the absence of known risk factors in case 1, supporting the idea that traditional risk factors for GBS disease are not causative, but rather identify groups of infants that are more likely to carry as-yet unidentified determinants of susceptibility. The present report also raises the question of whether EOD and LOD, different in terms of source of infection, route of transmission, risk factors, age at onset, clinical manifestations, and prevention possibilities, are two sides of the same coin; i.e., they are epidemiologically distinct conditions sharing the same molecular disease pathways.

It is important to anticipate here that any disease-causing allele identified in this family would be exceedingly rare in the general population, given its potential lethality early in life following natural exposure to GBS, a ubiquitous pathogen. Genetic defects will probably account for a minority of cases of sporadic GBS

disease. Other non-genetic molecular mechanisms will probably explain the susceptibility to GBS disease in the majority of individuals. A comprehensive understanding of all of the mechanisms underlying this enigmatic disease is required to develop cost-effective preventive strategies for those at the most vulnerable ages.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijid.2016.08.010>.

## References

- Centers for Disease Control and Prevention. Guidelines for the prevention of perinatal group B streptococcal disease. *Morb Mortal Wkly Rep* 2010;**59**: 1–32.
- Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, et al., on behalf of the PHLS (Public Health Laboratory Service) GBS Working Group. Group B streptococcal disease in UK and Irish infants younger than 90 days. *Lancet* 2004;**363**:292–4.
- Krause JC, Ghandil P, Chrabieh M, Casanova JL, Picard C, Puel A, et al. Very late-onset group B Streptococcus meningitis, sepsis, and systemic shigellosis due to interleukin-1 receptor-associated kinase-4 deficiency. *Clin Infect Dis* 2009;**49**: 1393–6.
- von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, et al. Pyogenic bacterial infections in humans with MyD88 deficiency. *Science* 2008;**321**:691–6.
- von Bernuth H, Ku CL, Rodriguez-Gallego C, Zhang S, Garty BZ, Marodi L, et al. A fast procedure for the detection of defects in toll-like receptor signaling. *Pediatrics* 2006;**118**:2498–503.