


# Primary pneumococcal peritonitis can be the first presentation of a familial complement factor I deficiency<sup>1</sup>

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Accepted for publication 22 June 2020

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<sup>1</sup>An abstract referring to the index patient has been previously presented at the 16th European Meeting of Complement in Human Disease, Copenhagen, Denmark, 8–12 September 2017, and has been published in the congress archives as Ugrinovic S, Gkrania-Klotsas E, Baxendale E, Firth H, Pritchard N, Mayer P, Kavanagh D, Lachmann P, Kumararatne D. A teenager with primary pneumococcal peritonitis. *Molecular Immunology* 89:156. <https://doi.org/10.1016/j.molimm.2017.06.116> ISBN: 0161-5890.

## Introduction

Primary pneumococcal peritonitis is an unusual clinical entity that has so far been described in liver disease, gastrointestinal surgical diseases and apparently healthy

## Summary

Primary pneumococcal peritonitis is a rare infection that has been described in women but has not been previously linked with immunodeficiency. The complement system plays a central role in immune defence against *Streptococcus pneumoniae* and, in order to evade complement attack, pneumococci have evolved a large number of mechanisms that limit complement-mediated opsonization and subsequent phagocytosis. We investigated an apparently immunocompetent woman with primary pneumococcal peritonitis and identified a family with deficiency for complement factor I. Primary pneumococcal peritonitis should be considered a possible primary immunodeficiency presentation.

**Keywords:** complement, immunodeficiency

immunocompetent young women, who occasionally also have an apparent genital focus of infection. Although it is a very rare presentation, it has not been previously linked with immunodeficiency. We investigated one such woman.

## Clinical history

A 16-year-old woman presented with a 4-day history of abdominal pain and signs of sepsis leading to a presumptive diagnosis of appendicitis. She was up to date with childhood vaccinations. She had not had a pneumococcal vaccine in childhood due to her age (routine childhood vaccination in England was introduced in 2006). On admission, her creatinine and haemoglobin were normal and she had an elevated neutrophil count of 21.4 (1.7–7.9  $10^9/l$ ) and a depressed lymphocyte count of 0.53 (1.2–5.0  $10^9/l$ ). Her past medical history was only notable for otitis media in childhood that had necessitated grommet insertion. During her appendectomy, frank intraperitoneal pus was identified. Histopathology of the removed appendix showed only marked serosal inflammation and a culture from an intra-operative swab grew *Streptococcus pneumoniae*, sensitive to penicillin on disc testing. A diagnosis of primary pneumococcal peritonitis was made. Her postoperative course was characterized by the development of intraperitoneal collections that necessitated draining and antibiotic treatment for a total of 6 weeks. Within the first 48 h of admission, she developed a normochromic normocytic anaemia with a haemoglobin of 102 (120–54 g/l) and thrombocytopenia. Four weeks later, she developed a widespread pruritic rash, renal dysfunction with a maximum creatinine of 236 (mmol/l), new proteinuria/microscopic haematuria, a mildly elevated alanine transaminase (ALT) and an eosinophilia of 1.7 (0.0–0.5  $10^9/l$ ), that resolved when piperacillin–tazobactam was discontinued, and were attributed to a drug reaction. Initial immunological investigations showed that she was HIV-negative by serology, had appropriately high immunoglobulin levels, a negative cryoglobulin screen and had normal lymphocyte phenotype analysis (data not shown). However, investigation of her complement system during convalescence was significant and showed normal immunoglobulins, reduced C3 with normal C4 and undetectable activity of the alternative complement pathway (AP50), with slightly reduced activity of the classical complement pathway (CH50) (Table 1). Detailed complement investigations revealed immunochemical and

functional deficiency of complement factor I (CFI) and reduction of factor B and factor H (Table 1).

The patient had low baseline pneumococcal serotype-specific antibodies consistent with her unvaccinated status (anti-pneumococcal antibodies were greater than 0.35  $\mu\text{g/ml}$  for two of 13 serotypes), but she mounted a good response to the conjugated pneumococcal vaccination (Prevenar13<sup>®</sup>, 10 of 13 serotypes as  $\geq 0.35 \mu\text{g/ml}$ ; data not shown). She was started on prophylaxis with penicillin V 500 mg twice per day and was immunized with the meningococcal B and the ACWY conjugate vaccines. Her family history was reviewed.

The patient was the third child of non-consanguineous parents. She had a 21-year-old sister, who had also had recurrent otitis media that necessitated grommet insertion in childhood, as well as a 17-year-old brother, who was asymptomatic. Both parents were well. Her paternal grandmother had rheumatoid arthritis. There was no family history of macular degeneration or of renal problems.

Since diagnosis the patient has remained on oral amoxicillin prophylaxis, but has suffered from otitis media with perforation and one episode of gastroenteritis. Her affected brother was also vaccinated and started on antibiotic prophylaxis and he remains well. Both parents were later found to have haploinsufficiency of CFI, which would put them at risk of atypical haemolytic uraemic syndrome and age-related macular degeneration and are under specialist clinical follow-up [1,2].

## Materials and methods – genetic analyses

Based on the complement investigations and finding of immunochemical and functional CFI deficiency, genetic analysis of the CFI gene (*CFI*) was undertaken as per Gleason [3].

## Results

She was found to be heterozygous for two *CFI* pathogenic mutations, c.772G>A p.(Ala258Thr) [1,4] and c.786del

**Table 1.** Summary of complement and genetic mutation analyses for the patient and the patient's family

Analyte	Proband	Mother	Father	Sister	Brother
C3 (0.75–1.65 g/l)	0.32	1.32	1.38	1.04	0.18
C4 (0.14–0.54 g/l)	0.13	0.19	0.17	0.14	0.16
CH50 (392–1019 $\mu\text{g/ml}$ )	263	660	580	496	250
AP50 (66–129 %)	0	106	92	64	0
Complement factor B (295–400 mg/l)	< 38	n.a.	n.a.	n.a.	< 38
Complement factor H (345–590 mg/l)	256	770	800	600	178
Complement factor I (38.0–58.0 mg/l)	< 2.4	18	11	9	< 2.4
Genotype, <i>CFI</i>	c772A/c786del	c772A/WT	WT/c786del	WT/c786del	c772A/c786del

AP50 = serum 50% haemolytic complement activity for the alternative pathway; C3 = complement factor 3; C4 = complement factor 4; *CFI* = complement factor I gene; CH50 = serum 50% haemolytic complement activity for the classical complement pathway; WT = wild-type; n.a. = not applicable.

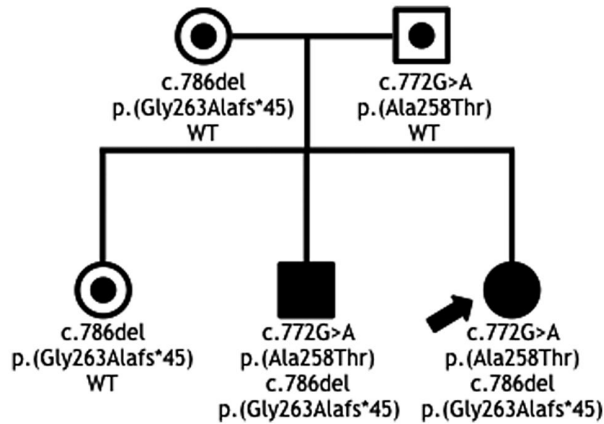


Fig. 1. Family pedigree. The index case is indicated by an arrow. WT = wild-type.

p.(Gly263Alafs\*45). Testing of parental DNA confirmed that she had inherited the *CFI* mutations on different alleles.

DNA analysis from the patient's brother showed that he was also heterozygous for the same two *CFI* pathogenic mutations. The patient's sister was heterozygous for only one of the two *CFI* pathogenic mutations, c.786del. The father was found to be heterozygous for c.772G>A and the mother heterozygous for c.786del.

The c.772G>A pathogenic mutation has previously been described in patients with atypical haemolytic uraemic syndrome [5] and age-related macular degeneration [1] and is associated with a low serum factor I level. The c.786del mutation has also been described previously in patients with atypical haemolytic uraemic syndrome and causes a frameshift which is predicted to result in the introduction of a stop codon further downstream (Gly263Alafs\*45) [6].

The family pedigree is shown in Figure 1.

## Discussion

*Streptococcus pneumoniae* is a common colonizer of the nasopharynx and is usually asymptomatic; however, in susceptible hosts it can cause otitis media, conjunctivitis, pneumonia, meningitis and septicaemia [7]. Complement activities such as opsonization and activation of inflammatory responses are central in the immune response against *S. pneumoniae* [8] and pneumococci have, as a result, developed many virulence factors that impair complement activity [9]. Polysaccharide vaccines have been proven effective against invasive disease [10]. Primary pneumococcal peritonitis is an unusual clinical entity. It is currently thought to represent three distinct clinical groups: (a) pneumococcal peritonitis associated with liver disease, infectious hepatitis, cirrhosis, ascites,

nephrotic syndrome, chronic renal failure and continuous ambulatory peritoneal dialysis, autoimmune disease or known immunocompromise including HIV [11], (b) pneumococcal peritonitis associated with gastrointestinal disease including appendicitis or after intra-abdominal surgery [12] and (c) pneumococcal peritonitis sometimes, but not always, presenting with an apparent genitourinary focus in otherwise healthy young women. We identified 40 published descriptions of the latter [13–17]. The fact that the disease is more common among women is thought to represent an infection source from the female genital tract or an ascending infection from the vagina: the latter is also supported by the fact that 13 of 40 women had an intrauterine contraceptive device (IUCD) in place, five of 40 were pregnant or postpartum and at least seven of 40 had a clinical diagnosis of pelvic inflammatory disease. Where described, all women had good short- to medium-term outcomes barring a relapse 6 weeks after completion of initial antibiotic treatment that responded to an IUCD removal and additional antibiotics. All were successfully treated with antibiotics, surgery, IUCD removal or a combination of the above. To our knowledge, none of these 40 women were investigated for immunodeficiency with the exception of two women who had an HIV test performed. It is arguable, therefore, if all the 40 cases truly represent pneumococcal peritonitis without a predisposing factor. However, as in our case, pneumococcal peritonitis can sometimes mimic appendicitis [17], so historical underdiagnosis in men and women is possible.

Our patient did not have a history of known comorbidities that would raise a primary immunodeficiency flag, but was identified to have a potentially life-threatening complement deficiency, with implications for other members of her family as well. *CFI* is one of the most important complement regulatory factors. In the presence of factor H (and other co-factors) it cleaves C3b to iC3b and in that way down-regulates the amplification loop of alternative pathway. *CFI* deficiency, therefore, prevents the generation of iC3b which is necessary for the recruitment of neutrophils which are needed for phagocytosis (Supporting information, Fig. S1). Until the present, there have been approximately 40 cases of *CFI* deficiency described in the literature. Total *CFI* deficiency leads to systemic consumption of C3, factor H and factor B due to uninhibited activation of alternative pathway. In the absence of *CFI*, there is no formation of iC3b. iC3b reacts with CR3 on neutrophils, and this reaction is essential for complement-mediated inflammation and opsonization [18,14].

Patients with complete *CFI* deficiency present with recurrent infections with encapsulated microorganisms (e.g. *Neisseria meningitidis*, *Haemophilus influenzae* and *S. pneumoniae*).

Patients with heterozygous CFI deficiency have a different phenotype and present with atypical haemolytic uraemic syndrome, C3 glomerulopathy and age-related macular degeneration [18,19]. The reason for this difference in clinical presentation is well understood [20]. If there is no CFI, no iC3b can be produced and no neutrophil activation can occur. These homozygotes are at risk of infection but not of immunopathology. Low levels of CFI allow iC3b to be formed, but give a reduced rate of C3b breakdown which increases activity of the alternative pathway and enhances the risk of immunopathology.

The index case presented here had not had a pneumococcal vaccine in childhood due to her age (routine childhood vaccination in England was introduced in 2006). We believe that the lack of protective pneumococcal antibodies coupled with lack of intact phagocytosis of pneumococci, which is highly dependent upon complement activation due to CFI deficiency, made her very susceptible to pneumococcal disease.

The management of infectious complications of complete CFI deficiency relies upon the optimization of vaccination against encapsulated bacteria and appropriate use of prophylactic antibiotics. As CFI synthesis occurs in the liver, bone marrow transplantation is not a strategy to correct CFI deficiency.

Alternative pathway complement disorders should be suspected when a patient has a low C3 and normal C4 quantification. Given our experience, and that both C3 and C4 measurements are readily accessible to clinicians, we propose that all future identified cases of pneumococcal peritonitis with no comorbidities or recurrent pneumococcal infections are investigated for primary immunodeficiency, including complement disorders. While this case has been in submission, a 2-year-old girl with primary pneumococcal peritonitis who also had CFI deficiency was identified [21]. We propose that the list of infectious diseases associated with disorders of complement henceforward includes unexplained pneumococcal peritonitis.

### Acknowledgements

E. G. K. conceived the paper. S. U., H. F. and D. K. performed the experiments. E. G. K. wrote the paper. All authors commented on the final manuscript and made valuable contributions. There was no financial contribution by any funder.

### Disclosures

The authors declare they have no financial or commercial conflicts of interest.

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### Supporting Information

Additional supporting information may be found in the on-line version of this article at the publisher's web site:

**Fig. S1.** CFI deficiency prevents the generation of iC3b which is necessary for the recruitment of neutrophils, needed for phagocytosis