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### ► To cite this version:

Claire Duployez, Caroline Loïez, Frédéric Wallet, Laure Marceau, Myriam Simon, et al.. When a *Neisseria meningitidis* PCR limitation contributes to an immunological disease diagnosis [Correspondence]. *Journal of Microbiology, Immunology and Infection*, 2024, 57 (2), pp.340-341. 10.1016/j.jmii.2023.10.009 . hal-04270102

**HAL Id: hal-04270102**

**<https://hal.science/hal-04270102v1>**

Submitted on 3 Nov 2023

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## Correspondence

# When a *Neisseria meningitidis* PCR limitation contributes to an immunological disease diagnosis

## KEYWORDS

Capsule;  
*Neisseria meningitidis*;  
 PCR;  
 16S rRNA gene  
 sequencing

Dear editor,

Capsulated *Neisseria meningitidis* is responsible for invasive meningococcal disease (IMD). Only few non-capsulated IMD are described in the literature.<sup>1,2</sup>

A 36-year-old patient, without previous medical history, presented for stiffness and headache. He had fever (39 °C), photophobia, vomiting, purpura on ankles and torso. Blood leukocyte count was  $29,98 \times 10^9$  cells/L (95.5 % polymorphonuclear), C-reactive protein 33.77 mg/dL, procalcitonin 18.4 ng/mL. He was given 2 g cefotaxime and 20 mg dexamethasone few hours before lumbar puncture and blood sample. Evolution was quickly favorable.

The cerebrospinal fluid revealed a leukocyte count of  $20,50 \times 10^9$  cells/L (92 % neutrophils), protein 729 mg/dL, glucose <4 mg/dL, lactic acid >16 mmol/L, and gram-negative diplococci were observed on the Gram stain. Blood and cerebrospinal fluid remained sterile. FilmArray® meningitis/encephalitis panel multiplex PCR (BioMérieux, Marcy l'Étoile, France) and *N. meningitidis* real-time PCR were negative. By 16S rRNA sequencing, a 677 bp DNA bacterial fragment was obtained and was 99.5 % identity with *Neisseria* sp. strains including *N. meningitidis*. The French National Reference Laboratory detected a non-capsulated *N. meningitidis* strain with two routinely used PCR: the *sodC* (Cu–Zn superoxide

dismutase, a generic conserved gene in *Neisseria meningitidis*) PCR was positive while the *ctrA* (capsule transport gene) PCR was negative, suggesting a capsule null locus (*cnl*) strain.<sup>3</sup> The strain belonged to the clonal complex CC175 (Table 1). This finding led us to look for other factors contributing to IMD such as underlying disease: only hypocomplementemia was detected (complement hemolytic 50 level <14 U/mL).

The major virulence factor leading to IMD is the polysaccharide capsule. Non-capsulated *N. meningitidis* strains can colonize nasopharynx of healthy subjects and are low-pathogenic strains, because not resistant to complement mediated lysis and opsonophagocytosis.<sup>3,6</sup> Few infection cases are reported in the literature, mostly in immunocompromised patients. In 2018, Kurose summarized 13 cases, including nine meningitis: three patients with C6 deficiency, one patient with IgG4-related disease, and five with unknown risk factor.<sup>6</sup>

Patients with a deficiency in the terminal complex and the factor properdin of the complement system have an increased risk of recurrent capsulated IMD. Less frequently, IMD caused by non-capsulated strains have been reported.<sup>7</sup> Rosain reported 61 IMD among subjects with terminal complement pathway deficiencies: 8 % were due to non-capsulated strains.<sup>2</sup> Ladhani described 20 IMD among patients with inherited and acquired complement deficiency: four among nine IMD in patients on eculizumab therapy were due to non-groupable or group E (less virulent) isolates.<sup>1</sup> Thus, it is necessary to investigate immune comorbidities after non-capsulated IMD.

The capsule being a virulence factor responsible for IMD, *ctrA* is frequently used to detect *N. meningitidis*, including in commercial PCR assays. Nevertheless, it has always been described that nucleotide substitution/rearrangement in *ctrA* gene may be responsible for false-negative results, including in invasive strains.<sup>4</sup> Carriage isolates may even lack this gene.<sup>5</sup> Then our last taking-home message is that

<https://doi.org/10.1016/j.jmii.2023.10.009>

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Please cite this article as: C. Duployez, C. Loïez, F. Wallet et al., When a *Neisseria meningitidis* PCR limitation contributes to an immunological disease diagnosis, Journal of Microbiology, Immunology and Infection, <https://doi.org/10.1016/j.jmii.2023.10.009>

**Table 1** Molecular biology tests performed on the cerebrospinal fluid sample.

Tests performed	Targets	Result
BioFire® FilmArray meningitis/encephalitis panel (BioMérieux, Marcy l'Étoile, France)	« Encapsulated <i>N. meningitis</i> (groups A, B, C, W, Y) and DNA from a strain with a variant <i>ctrA</i> gene »	Not detected
<i>N. meningitidis</i> real-time PCR (Diagenode Diagnostics, Liège, Belgium)	<i>ctrA</i> (capsule transport in encapsulated strains) <i>csaB</i> (group A) <i>csb</i> (group B) <i>csc</i> (group C) <i>csw</i> (group W) <i>csy</i> (group Y)	Not detected
16S rRNA sequencing (377 ABI Prism; PE Applied Biosystems, Foster City, CA., USA) Analysis with BLAST system	Universal 16S RNA PCR	<i>Neisseria</i> sp.
<i>sodC</i> and <i>ctrA</i> real-time PCR (Centre National de Référence des méningocoques, Institut Pasteur, Paris, France)	<i>sodC</i> (Cu–Zn superoxide dismutase gene) <i>ctrA</i> (capsule transport in encapsulated strains)	Detected Not detected
MLST (Centre National de Référence des méningocoques, Institut Pasteur, Paris, France)	Multilocus sequence typing	Clonal complex CC175
Final result		Non-capsulated <i>N. meningitidis</i>

biological tests cannot be 100 % sensitive. This warrants a systematic *sodC* PCR in addition to *ctrA* PCR since *sodC* is conserved in *N. meningitidis* strains regardless of capsule status but not in other *Neisseria* species.<sup>5</sup> Presume meningococcal disease with negative PCR may be due to a cnl strain and clinical history remains the best indicator for diagnosis.

## Declaration of competing interest

None.

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18 August 2023  
Available online ■ ■ ■