Dear Editor, Deficiencies of early components of the classical complement pathway are associated with an increased risk of SLE. There is a hierarchy of disease susceptibility and severity according to the position of the deficient protein in the classical complement pathway. SLE penetrance in C1q deficiency is 90%, and patients generally present with severe disease, whereas only 10–20% of C2-deficient patients develop SLE, with a disease severity comparable to sporadic SLE [1, 2]. C1q inhibits type I IFN (T1IFN) release, and its deficiency is associated with upregulated T1IFN signalling [3, 4]. Increased T1IFN signalling in C1q deficiency is proposed to explain the association with SLE [3]. It is unknown whether T1IFN signalling is also increased in other, more common early complement deficiencies, such as C2 deficiency (estimated prevalence in European population 1 in 20,000) [2]. We identified only one C2-deficient patient in the literature for whom T1IFN signalling was assessed [4]. In the present report, we investigate the association between C2 deficiency, T1IFN signalling and autoimmunity in a kindred with C2 deficiency and primary SS (pSS). The UZ/KU Leuven ethics committee approved this study (SS2653).

The index patient was born to consanguineous parents of Moroccan descent (Fig. 1A). Her mother and two younger brothers (II.3 and II.4) were healthy. Her father suffered from adult-onset autoantibody-negative type I diabetes. Her older sister (II.1) carried a de novo deletion in chromosome 4p. At age 9 years, the index patient presented with oligo-arthritis of both knees and ankles. Her medical history mentioned two episodes of ethmoiditis with orbital cellulitis at age 2.5 and 4 years. Laboratory examination revealed high IgG (2390 mg/dl; normal range: 483–1548 mg/dl), slightly elevated ESR (26 mm/h; normal range: 1–15 mm/h) and amylase levels (158 U/l; normal range: 28–100 U/l), low memory B cells (2.4%), RF positivity (468 IU/ml; normal: <40 IU/ml) and anti-SS-A/Ro60 (>240 IU/ml; normal: <7 U/ml) antibodies. Total complement activity was low (27%; normal range: 70–140%), with borderline C4 (0.15 g/l; normal range: 0.16–0.38 g/l) and undetectable C2 (<7 mg/l; normal range: 14–25 mg/l). MRI showed mild inflammatory lesions in the right parotid gland. Based on this presentation, the tentative diagnosis of pSS was made. By age 10 years, the patient showed recurrent transient arthritis, with cutaneous vasculitis affecting the legs, arms, back and eyelids, xerostomia and dental caries. Autoantibodies remained positive, and total complement activity (<20%) and C2 (<7 mg/l) remained low during follow-up. At the age of 12 years, she was started on HCQ 200 mg/daily, resulting in clinical remission.

Whole-exome sequencing of the patient, her parents and healthy brother II.3 identified a 28 bp deletion in C2, known to cause type I C2 deficiency [2]. The mutation was heterozygous in the parents and homozygous in the index patient and brother II.3. Confirmatory Sanger sequencing also revealed C2 deficiency in sister II.1 (Fig. 1A). Homozygosity segregated with low total complement activity and undetectable C2 levels, whereas the heterozygous parents had normal total complement activity and only slightly reduced C2 (Fig. 1B). Interestingly, we detected anti-SS-A/Ro60 antibodies in sister II.1, showing that both C2-deficient sisters have autoantibodies.

Next, we assessed a seven-gene T1IFN score in all available family members and compared them with 10 healthy controls (Fig. 1C; Supplementary Data S1, available at Rheumatology Advances in Practice online). In the three family members without autoantibodies (I.1, I.2 and II.3), the T1IFN score did not differ from healthy controls. Strikingly, the index patient and sister II.1 had drastically elevated T1IFN scores (Fig. 1C).

We re-examined the whole-exome sequencing data to identify variants of interest with the potential to contribute to the high T1IFN signature and autoantibody production in the C2-deficient sisters (i.e. present in index and not present in parents and C2-deficient brother). None of the identified variants were autoimmunity susceptibility or T1IFN-related genes, providing no additional candidates for disease risk modulation (Supplementary Data S2, available at Rheumatology Advances in Practice online).

This is the first report of pSS associated with C2 deficiency and high T1IFN signalling. The diagnostic tests to meet the 2016 ACR/EULAR classification criteria are not performed universally in children, as in this case [5]. Nevertheless, the diagnostic findings were deemed sufficient to diagnose pSS in a child presenting with arthritis, cutaneous lesions and xerostomia. Secondary SS has been reported in C1q, C2 and C4 deficiency [2, 6]. High T1IFN signalling potentially impacts the clinical phenotype of pSS, because cutaneous vasculitis is a prominent feature.

Key message

- C2 deficiency is associated with high type I IFN signalling and autoimmunity.
feature of type I interferonopathies, but occurs in only <10% of paediatric pSS patients [5, 7].

In this kindred, both C2-deficient sisters harbour autoantibodies and high T1IFN signalling. High T1IFN signalling has been reported in patients with C1q deficiency and in one C2-deficient patient, and early complement deficiency is being considered as a cause of autoimmune interferonopathy [3, 4, 7]. The link between early complement deficiency and T1IFN signalling is still under investigation and might involve uncleared neutrophil extracellular traps serving as a source of interferogenic autoantigens, thus fuelling a T1IFN amplification loop [7, 8]. Consequently, patients with early complement deficiency and signs of autoimmunity might benefit from therapies that inhibit T1IFN signalling (e.g. HCQ and Janus kinase inhibitors) [9]. Our findings further support the observation that female sex is associated with increased T1IFN signalling, potentially contributing to the susceptibility of females to autoimmunity, also in the context of C2 deficiency [10].

Together, we provide evidence for an association between C2 deficiency, autoimmunity and high T1IFN signalling. C2-deficient patients are potentially at risk of developing secondary autoimmune interferonopathies, including pSS, and might benefit from therapies targeting T1IFN signalling.

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Data availability statement
All data are available upon request via contacting the authors Mathijs Willemsen and Carine Wouters.

Supplementary data
Supplementary data are available at Rheumatology Advances in Practice online.

Mathijs Willemsen1,2,
Erika Van Nieuwenhove1,2,3,
Nasim Sadat Seyed Tabib4, Frederik Staels3,5,
Rik Schrijvers5, Lien De Somer3,
Adrian Liston1,2,7,*, Stephanie Humblet-Baron1,2,*, and Carine Wouters3,*

1Laboratory of Adaptive Immunity, Department of Microbiology, Immunology and Transplantation, KU Leuven,
2VIB-KU Leuven Center for Brain and Disease Research,
3Division Pediatric Rheumatology, Department of Pediatrics, University Hospitals Leuven,
4Department of Chronic Diseases, Metabolism and Ageing, TARGID, KU Leuven,
5Allergy and Clinical Immunology Research Group, Department of Microbiology, Immunology and Transplantation, VIB-KU Leuven Center for Brain and Disease Research, KU Leuven, Leuven, Belgium
6Laboratory of Immunobiology, Department of Microbiology, Immunology and Transplantation, Rega Institute for Medical Research, KU Leuven, Leuven, Belgium
7Laboratory of Lymphocyte Signalling and Development, The Babraham Institute, Cambridge, UK

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Correspondence to: Carine Wouters, Department of Pediatric Rheumatology, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium. E-mail: carine.wouters@uzleuven.be

*Adrian Liston, Stephanie Humblet-Baron and Carine Wouters contributed equally to this study.

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Letter to the Editor