RHEUMATOLOGY ADVANCES IN PRACTICE

Letter to the Editor (Case report)

Rheumatology Advances in Practice 2022;00:1–2
https://doi.org/10.1093/rap/rkac018
Advance access publication 21 March 2022

Primary Sjögren's syndrome and high type I interferon signalling in a kindred with C2 deficiency

Key message

- C2 deficiency is associated with high type I IFN signalling and autoimmunity.

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 (S52653).

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: $\leq$40 IU/ml) and anti-SS-A/Ro60 ($>$240 U/ml; normal $\leq$7 U/ml) antibodies. Total complement activity was low (27%; normal range: 70–140%), with borderline C4 (0.15 g/l; normal range: 0.16–0.38 g/l) and undetectable C2 ($<$7 mg/l; normal range: 14–25 mg/l). MRI showed mild inflammatory lesions in the right parotid gland. Based on this presentation, the tentative diagnosis of pSS was made. By age 10 years, the patient showed recurrent transient arthritis, with cutaneous vasculitis affecting the legs, arms, back and eyelids, xerostomia and dental caries. Autoantibodies remained positive, and total complement activity ($<$20%) and C2 ($<$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.

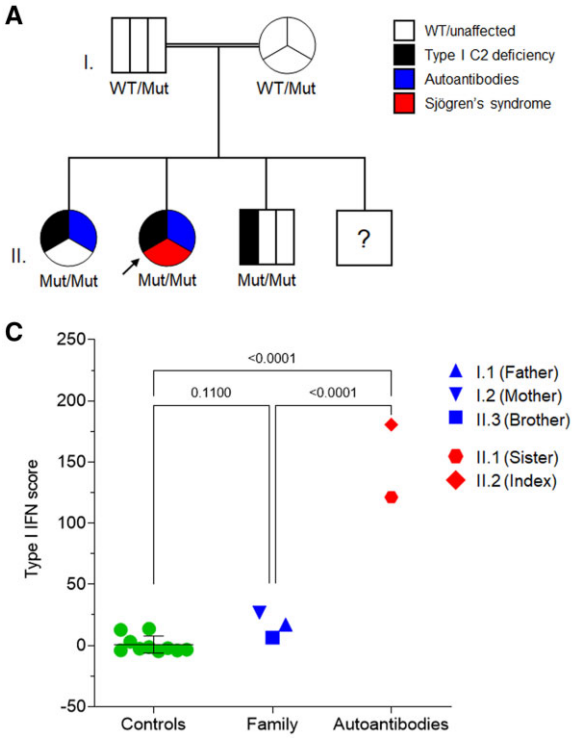
Whole-exome sequencing of the patient, her parents and healthy brother II.3 identified a 28 bp deletion in *C2*, known to cause type I C2 deficiency [2]. The mutation was heterozygous in the parents and homozygous in the index patient and brother II.3. Confirmatory Sanger sequencing also revealed C2 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 bother). 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

FIG. 1 Association between type I C2 deficiency, autoantibodies and type I interferon score



B

	Index	I.1	I.2	II.1	II.3	Reference
Age (years)	9	45	36	16	12	
Complement						
Total complement activity	27	109	113	<20	<20	70-140%
C1q	0.19	0.26	0.21		0.21	0.10-0.25 g/L
C2	<7	12	11	<7	<7	14-25 mg/L
C3	1.28	0.91	1.02	1.17	0.89	0.79-1.52 g/L
C4	0.15	0.19	0.19	0.18	0.14	0.16-0.38 g/L
C5		0.16	0.19	0.17	0.11	0.12-0.16 g/dL
Autoimmune serology						
SS-A/Ro60	>240	<0.4	<0.4	238	<0.4	≤6.9 U/mL
Rheumatoid factor	468	<20	<20	<20	<20	≤40 IU/mL

(**A**) Kindred. (**B**) Clinical complement and autoimmune serology studies performed in available family members. (**C**) Type I interferon score of controls ($n = 10$), unaffected family members ($n = 3$) and family members with autoantibodies ($n = 2$). Data were analysed (GraphPad v.9.0.0) using a one-way ANOVA with Holm–Šídák correction for multiple comparison. $P < 0.05$ was considered significant.

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.

Acknowledgements

C.W., A.L. and S.H.-B. conceptualized and supervised the study. C.W. and L.D.S. collected clinical data. E.V.N. and N.S.S.T. performed wet lab experiments. M.W. and E.V.N. performed genetic analysis. M.W. and F.S. drafted the manuscript. All authors were involved in revising the manuscript critically for important intellectual content, and all authors approved the final version to be published.*Patient consent:* All study participants provided written informed consent.

Funding: This work was supported by the KU Leuven (C1 grant C16/17/010). E.V.N. (1S22716N) and F.S. (11B5520N) are fellows of the Fonds Wetenschappelijk Onderzoek—Vlaanderen National Fund for Scientific Research (FWO). R.S. (1842929N) is an FWO senior clinical investigator fellow. C.W., L.D.S. and R.S. are members of the European Reference Network for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (Project ID No. 739543).

Disclosure statement: The authors have declared no conflicts of interest.

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 Willemsen[1,2], Erika Van Nieuwenhove[1,2,3], Nasim Sadat Seyed Tabib[4], Frederik Staels[1,2,5], Rik Schrijvers[5], Lien De Somer[3], Adrian Liston[1,2,7,*], Stephanie Humblet-Baron[1,2,*] and Carine Wouters[3,*]

[1]*Laboratory of Adaptive Immunity, Department of Microbiology, Immunology and Transplantation, KU Leuven,* [2]*VIB-KU Leuven Center for Brain and Disease Research,* [3]*Division Pediatric Rheumatology, Department of Pediatrics, University Hospitals Leuven,* [4]*Department of Chronic Diseases, Metabolism and Ageing, TARGID, KU Leuven,* [5]*Allergy and Clinical Immunology Research Group, Department of Microbiology, Immunology and Transplantation,* [6]*Laboratory of Immunobiology, Department of Microbiology, Immunology and Transplantation, Rega Institute for Medical Research, KU Leuven, Leuven, Belgium and* [7]*Laboratory of Lymphocyte Signalling and Development, The Babraham Institute, Cambridge, UK*
Accepted 23 February 2022
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.

References

1 Omarjee O, Picard C, Frachette C *et al.* Monogenic lupus: dissecting heterogeneity. Autoimmun Rev 2019;18:102361.

2 Jönsson G, Sjöholm AG, Truedsson L *et al.* Rheumatological manifestations, organ damage and autoimmunity in hereditary C2 deficiency. Rheumatology (Oxford) 2007;46:1133–9.

3 Wolf C, Brück N, Koss S *et al.* Janus kinase inhibition in complement component 1 deficiency. J Allergy Clin Immunol 2020;146:1439–42.e5.

4 Rice GI, Melki I, Frémond ML *et al.* Assessment of type I interferon signaling in pediatric inflammatory disease. J Clin Immunol 2017;37:123–32.

5 Basiaga ML, Stern SM, Mehta JJ *et al.*; Childhood Arthritis and Rheumatology Research Alliance and the International Childhood Sjögren Syndrome Workgroup. Childhood Sjögren syndrome: features of an international cohort and application of the 2016 ACR/EULAR classification criteria. Rheumatology (Oxford) 2021;60:3144–55.

6 Levy D, Craig T, Keith PK *et al.* Co-occurrence between C1 esterase inhibitor deficiency and autoimmune disease: a systematic literature review. Allergy Asthma Clin Immunol 2020;16:41.

7 Kim H, Sanchez GA, Goldbach-Mansky R. Insights from Mendelian interferonopathies: comparison of CANDLE, SAVI with AGS, monogenic lupus. J Mol Med (Berl) 2016;94:1111–27.

8 d'Angelo DM, Di Filippo P, Breda L *et al.* Type I interferonopathies in children: an overview. Front Pediatr 2021;9:631329.

9 Seror R, Nocturne G, Mariette X. Current and future therapies for primary Sjögren syndrome. Nat Rev Rheumatol 2021;17:475–86.

10 Webb K, Peckham H, Radziszewska A *et al.* Sex and pubertal differences in the type 1 interferon pathway associate with both X chromosome number and serum sex hormone concentration. Front Immunol 2018;9:3167.