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CD21 deficiency in two siblings with recurrent respiratory infections and hypogammaglobulinemia

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33 *To the Editor,*

34

35 The complement system plays a major role in humoral immunity via activation of the
36 classical pathway and the development of adaptive responses. This function is ensured
37 principally by CD21 (or CR2), a receptor that recognizes C3 cleavage fractions containing a
38 C3d moiety bound to an antigen¹. CD21 is primarily expressed by follicular dendritic cells
39 (FDC) and B cells. The CD21 on FDCs traps soluble C3d-bound antigens for their
40 presentation to B cells in the lymphoid tissues. The CD21 on B cells forms part of the CD19
41 complex, along with CD81, CD225 and CD19, and acts as a coreceptor for the B-cell receptor
42 (BCR)-Igαβ. The coligation of a C3d-bound antigen to the BCR and CD21 increases the
43 strength of the activating signal delivered to B cells¹. Only two patients with a common
44 variable immunodeficiency syndrome (CVID) phenotype caused by autosomal recessive
45 CD21 deficiency have been reported to date^{2,3}. We report here the first multiplex kindred with
46 CD21 deficiency.

47 The two siblings were born to consanguineous French parents (**Figure E1**). The proband (P1),
48 a 14-year-old girl, was first referred at the age of seven years, for recurrent otitis media and
49 bronchitis, which persisted despite three adenoidectomies and multiple grommet insertions.
50 She also had undocumented lobar pneumonia at the age of 12 years. Immunological tests
51 performed at the age of seven years revealed low levels of immunoglobulin (Ig) G1, resulting
52 in low levels of IgG. IgG and IgG1 levels were normal at the age of 10 years. IgG to tetanus
53 and diphtheria were reduced despite routine immunization (**Table E1**). This patient developed
54 partial conductive deafness, despite the systematic treatment of otitis media with antibiotics.
55 Histological analysis of an adenoid sample showed a hypertrophic mucosa with florid
56 hyperplasia of the secondary lymphoid follicles. Germinal centers contained large numbers of
57 macrophages, the cell bodies of which were readily stained. Interfollicular areas contained

58 lymphocytes, marginal cells, immunoblasts and plasmocytes, with no cellular atypia (**Figure**
59 **E2**). P1's 11-year-old brother (P2) was first referred at the age of five years, for recurrent
60 otitis media, rhinopharyngitis and bronchitis, which have begun at the age of four months. He
61 underwent one adenoidectomy and two grommet insertions. Initial immunological
62 explorations showed normal levels of IgG but slightly low levels of IgG1. P2 then developed
63 mild hypogammaglobulinemia between the ages of 7 and 11 years. IgG to tetanus and
64 diphtheria were reduced despite routine immunization. After booster injections, the titers of
65 antibodies specific for tetanus toxoid reached protective levels in the two patients, whereas
66 those for anti-diphtheria toxoid antibodies remained low (**Table E1** and **Figure E2**). None of
67 the two patients received immunoglobulin substitution. P1 received prophylaxis by
68 cotrimoxazole during one winter season at the age of 7 which reduced the frequency of
69 infections. A flow-cytometry study of B cells from the two patients showed a decrease in
70 class-switched memory B cells and a complete loss of CD21 cell surface expression (**Figure**
71 **E1**). CD21 immunohistochemistry of the adenoid tissue of P1 revealed a complete absence of
72 staining (**Figure E2**). Genomic sequencing of *CR2*, the gene encoding CD21, revealed a
73 homozygous one-base pair deletion (c.234delC) predicted to lead to a frameshift and the
74 insertion of a premature stop codon (p.T209HfsX10) (**Figure E1**). Both parents were
75 heterozygous for this mutation. The father was asymptomatic and had a normal
76 immunophenotype, with slightly lower levels of CD21 expression on B cells than observed in
77 the healthy control (**Figure E1**). The mother was asymptomatic but had had recurrent otitis
78 media during childhood. Laboratory assessments revealed profound B lymphopenia (0.9%;
79 $3/\text{mm}^3$), but normal levels of immunoglobulins and a protective titer of antibodies against
80 toxoid tetanus in the mother at the age of 35 years.

81 We report here complete CD21 deficiency due to a new homozygous *CR2* mutation in two
82 siblings. Both patients were referred for recurrent upper respiratory tract infections beginning

83 in early childhood. Both have mild hypogammaglobulinemia and low levels of memory class-
84 switched B cells, with impaired production of antibodies specific for certain protein antigens.
85 The adenoid tissue of P1 had hyperplastic germinal centers with a normal architecture but no
86 CD21-positive FDCs. The number and size of germinal centers within splenic follicles are
87 smaller after immunization in *cr2*^{-/-} mice than in wild-type mice⁴, probably because *cr2*^{-/-} mice
88 are also CD35-deficient¹. CD35 is another receptor of cleaved complement fractions⁴. Only
89 two other CD21-deficient patients have been described to date^{2,3}. Both have mild
90 hypogammaglobulinemia associated with low levels of memory B cells, but they have a
91 normal antibody response to protein antigens^{2,3} (**Table 1**). The first patient reported was
92 diagnosed at the age of 26 years. He had recurrent upper respiratory tract infections before the
93 age of six years and remained asymptomatic for 20 years following adenoidectomy². At the
94 age of 26 years, he developed symptoms suggestive of COVID. The second reported case was a
95 16 year old boy with a history of autoimmune disease with no history of recurrent infection³.
96 The two patients reported here had more severe clinical and immunological phenotypes than
97 the first two patients to be described^{2,3} (**Table 1**). As our patients were born to
98 consanguineous parents, we cannot rule out the existence of other pathogenic variants in their
99 genomes, although laboratory investigations detected no other immunological abnormality.
100 Low levels of calcium flux have been reported in CD21-deficient B cells exposed to a
101 suboptimal quantity of C3d-bound antigen². This finding suggests that the impaired B-cell
102 response in CD21-deficient patients is due to decreased stimulation of B cells from the
103 germinal center in the absence of positive signals mediated via the CD21 coreceptor¹. The
104 absence of CD21 expression on FDCs may also be responsible for impaired antigen retention
105 in lymphoid follicles. Taken together, these data suggest that the absence of CD21 expression
106 on B cells and FDCs could lead to an inability to sustain specific humoral responses after
107 antigen challenge. This finding highlights the importance of CD21 for the development of

108 humoral adaptive immunity and the induction of memory B cells in humans. CD21 deficiency
109 may however be surmountable in case of high concentration or repeated antigen exposure².
110 Other deficiencies in components of the CD19 complex (CD19 and CD81 deficiencies) are
111 also associated with an impaired response to protein antigens, albeit with a more severe
112 clinical and immunological phenotype than in CD21 deficiency^{3,5-9}. This underlie that CD21
113 may be more redundant than CD19 and CD81. Additional clinical reports for CD21-deficient
114 patients and their long term follow-up are now required to improve our understanding of the
115 natural course of this deficiency. The defect observed in these patients could easily be
116 screened by flow cytometry panel for CVID, which should be offered to patients with an
117 impairment of humoral immunity.

118

119

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Table 1 – Clinical, immunological and genetic characteristics of CD21-deficient patients

	Thiel <i>et al.</i>, 2012²	Wentink <i>et al.</i>, 2015³	P1	P2
Age at diagnosis	26 y	13 y	14 y	11 y
Sex	M	M	F	M
Country of residence	Germany	The Netherlands	France	France
Consanguinity	No	No	Yes	Yes
Clinical history	< 6 y: URT infections 6 – 26 y: asymptomatic 26 y: URT and LRT infections, SMG, diarrhea, fever	No recurrent infection Possible autoimmune disease	Recurrent URT and LRT infections since early childhood	Recurrent URT infections since early childhood
CR2 mutations	c.1225+1G>C/ p.W766X	p.R142X/ p.I926SfsX14	p.T209HfsX10/ p.T209HfsX10	p.T209HfsX10/ p.T209HfsX10
Immunophenotyping				
CD21 expression	Absent	Absent	Absent	Absent
Class-switched memory B cells	Decreased	Decreased	Decreased	Decreased
Immunoglobulin				
IgG	Low	Low	Low to normal	Low to normal
IgA	Low	Low	Normal	Normal
IgM	Normal	Low	Normal	Subnormal
Serology				
Protein antigens	Normal	Normal	Low	Low
Polysaccharide antigen	Low	Normal	Normal*	Low*

*assessed by blood group isohemagglutinin production; URT: upper respiratory tract; LRT: lower respiratory tract; SMG: splenomegaly