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Letter to Editor

Aichivirus: an Emerging Pathogen in Patients with Primary and Secondary B-Cell Deficiency

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Aichivirus **AQ1** was **AQ2** initially reported in 1989 [1]. Aichivirus belongs to the Kobuviruses, members of the growing family of Picornaviridae. Additional Kobuviruses, including Aichivirus-like Kobuviruses, have been detected in dogs, swine, and cattle. Aichivirus occurs globally, and serological studies have indicated that 80 to 95% of individuals have been exposed or infected by the age of 40 years [1]. Aichivirus has been identified in sewage waters and marine bathing and non-bathing waters. Aichivirus A predominates, but Aichivirus B is evolving as the dominant Aichivirus in the Netherlands and in China. In healthy individuals, Aichivirus replicates in the gastrointestinal tract and can cause self-limiting gastroenteritis with low incidences found in tested cohorts of healthy children (around 1% of tested samples) [1]. However, reports from gastroenteritis outbreaks have reported higher incidences of up to 30% of diarrhea samples. Aichivirus genomes are enriched in stool samples from human immunodeficiency virus (HIV)-infected individuals, pointing to Aichivirus opportunistic pathogen in HIV infection [2].

Recently, we have described Aichivirus A as the cause of disseminated infection in a patient with X-linked agammaglobulinemia (XLA) who had been stable on immunoglobulin treatment. During a summer vacation in Italy, he presented with acute febrile, diarrheal illness, followed by new-onset seizures, recurrent fevers, progressive hepatosplenomegaly, bilateral renomegaly, progressive pancytopenia, and renal failure. Initially, the suspicion was that the patient was suffering from renal T-cell lymphoma. A viral etiology was suspected because of the acute onset and the changing V beta repertoire of CD8+ T cell infiltrates in sequential kidney biopsies. In the peripheral blood, an exhausted T-cell phenotype was identified. Aichivirus A was detected by RNA metagenomics of a renal biopsy and confirmed by PCR of spleen, urine, feces, and sputum, highlighting the potential of this virus to cause extra-intestinal disseminated disease [3]. Following hematopoietic stem-cell transplantation (HSCT), the patient cleared the virus, although he developed severe graft-versus-host disease and continues to have chronic kidney disease 6-year post-HSCT [4]. A second report describes an unrelated XLA patient with fever and progressive kidney enlargement with—monoclonal CD8+ T-cell infiltration, also present in the bone marrow and skin biopsies. Aichivirus was detected by metagenomic sequencing of the skin biopsy, and the patient received HSCT from a haploidentical donor with excellent recovery. His skin disease resolved, but no formal virology assays were performed to prove clearance of the virus. This patient also continues to have CKD, 1-year post-HSCT [5]. This emerging phenotype of Aichivirus infection in XLA is one of acute gastroenteritis, followed by hepatosplenomegaly and bilateral renomegaly mimicking renal lymphoma.

These two reports jointly point to Aichivirus as an opportunistic pathogen for patients with X-linked agammaglobulinemia [3, 5]. Both patients were on IgG substitution at the time of infection. Despite the high seroprevalence of Aichivirus in adults, these cases suggest that no or insufficient passive protection was provided by the Ig substitution. We have now also detected Aichivirus infection and persistence in tissue (spleen) and/or fecal samples from at least two additional patients who developed secondary B-cell lymphopenia following treatment with rituximab (personal observation, Isabelle Meyts, Giorgia Bucciol, Elke Wollants, Katrien Jansen). One patient, a 13-year-old girl, developed progressive hepatosplenomegaly and renomegaly following rituximab treatment for anti-aquaporine 4 (+) neuromyelitis optica. A second patient, a 6-year-old boy, received rituximab for auto-immune encephalitis and was tested for Aichivirus when he developed bilateral kidney enlargement and splenomegaly. Aichivirus was detected in a liver and spleen biopsy of the first patient and on stool samples by polymerase chain reaction for both patients. For the second patient, no biopsy specimen was available. Upon restoration of B cells, the Aichivirus infection resolved in patient 2, and the renomegaly and splenomegaly are regressing (Table 1). These observations suggest that Aichivirus represents an emerging opportunistic pathogen in patients affected by primary or secondary B-cell lymphopenia and hypogammaglobulinemia (Fig. 1).

Table 1

Clinical data of the patients with secondary B-cell deficiency and Aichivirus infection **AQ3**

Patient 1 events and treatment								
Age	8 years	9 years	11 years	12 years	13 years	13, 5 years		
Event	NMO	2nd NMO episode	Myelitis; gastroenteritis*	Transverse myelitis; colitis				
Treatment	Pulse steroids	Pulse steroids	Pulse steroids	Pulse steroids				
Treatment	Mycophenolate mofetil							
Treatment		Rituximab/6 months + IVIG/4 weeks						
				Sirolimus				
Igs and B cells								
IgG (5.3–13 g/l)	~~nd~~ND	6.89	10.5	9.69	7.29			
IgA(0.6–2.7 g/l)	~~nd~~ND	0.19	0.17	0.14	0.13			
IgM(0.43–1.73 g/l)	~~nd~~ND	0.36	0,32	0.27	0.25			
B cells/mcl		0 (post-rituximab)	0	0,004	0	0.002		
Ultrasound	~~nd~~ND			« colitis »				
Spleen (SD)			+6.9	+10.6		+12.7		
Liver (SD)			+4	+5.6		+9		
Right kidney (SD)			+0.67	+12.4		+5		
Left kidney (SD)			+2	+12		+6		
Aichivirus PCR						+ on renal biopsy, spleen biopsy, and stool		

*Suspected time of Aichivirus infection, no other causative agent found

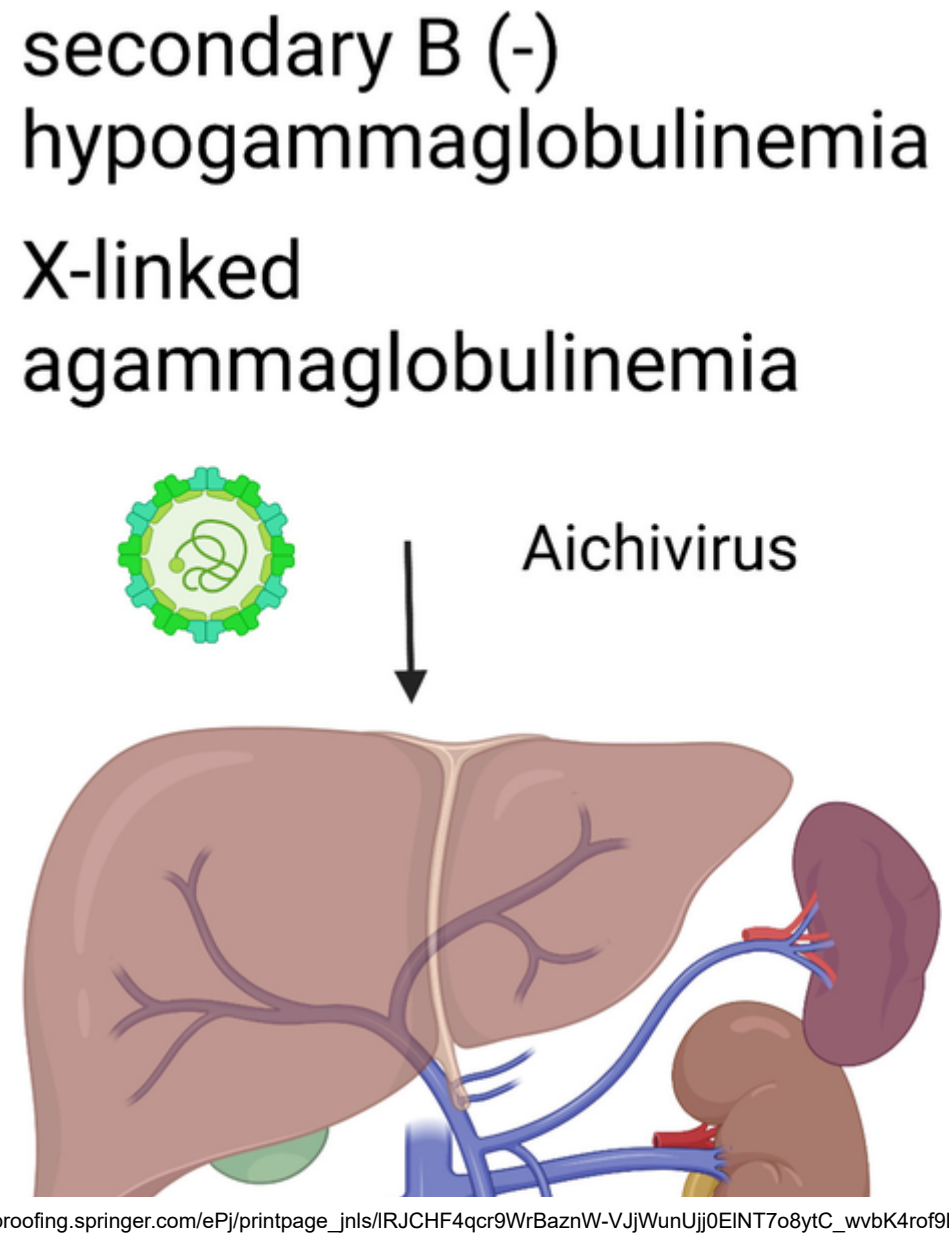
~~*nd*~~*ND*, no done; *SD*, standard deviation from age specific organ size as per ultrasound; *mcl*, microliter; *abs*, antibodies; *IVIG*, intravenous immunoglobulin treatment; *MOG*, myelin oligodendrocyte glycoprotein

For IgG, IgA, and IgM, age-specific and lab-specific reference ranges are provided between brackets

Patient 2 events and treatment								
Age	5 years 9 monts	5 years 10 months	5 years 11 months	6 years	6 years 2 weeks	6 years 1 month	6 years 2 monts	6 years 3 months
Event	Acute auto-immune encephalitis (MRI suggestive of viral encephalitis)	Result: anti-MOG abs (+)	Abdominal pain, vomiting and diarrhea * +++, ultrasound shows colitis					
Treatment	Pulse steroids with taper over 4 weeks							
Treatment	Plasmapheresis 10×							
Treatment		Rituximab single dose						
Treatment		IVIG/4 weeks						
Igs and B cells								
IgG (5.1–12.5 g/l)	~~nd~~ND	0.34*	2.19	~~nd~~ND	3.27	3.93	4.8	4.4
IgA(0.29–3.8 g/l)	~~nd~~ND	0.19*	0.23	~~nd~~ND	0.31	0.22	0.21	0.2
IgM(0.34–1.42)	~~nd~~ND	0.36*	0.1	~~nd~~ND	0.12	0.009	0.11	0.11
B cells/mcl		1281 (prior to rituximab)	0 (post-rituximab)	~~nd~~ND	0.003	0.001	0.312	0.542
Ultrasound	~~nd~~ND		« colitis »		~~nd~~ND	~~nd~~ND		
Spleen (SD)			~~nd~~ND	+0.1			−0.2	
Liver (SD)			−1.6	+2.6			−0.9	
Right kidney (SD)			−1.6	+4.1			+1.9	
Left kidney (SD)			−1.6	+2.3			0	
Aichivirus PCR stool				(+)			(−)	
*Suspected time of Aichivirus infection, no other causative agent found								
~~*nd*~~*ND*, no done; *SD*, standard deviation from age specific organ size as per ultrasound; *mcl*, microliter; *abs*, antibodies; *IVIG*, intravenous immunoglobulin treatment; *MOG*, myelin oligodendrocyte glycoprotein								
For IgG, IgA, and IgM, age-specific and lab-specific reference ranges are provided between brackets								

Fig. 1

Primary or secondary B-cell lymphopenia and hypogammaglobulinemia



While there is no known effective anti-viral treatment for Aichivirus, it is possible that repurposing of drugs used in other RNA virus infections, including picornavirus, may be effective, but they have yet to be tried. Neither high-dose intravenous immunoglobulin infusions nor immunosuppression or T-cell depletion proved effective in treating the infection. The latter treatment was used under the suspicion that the ongoing T-cell inflammation caused the irreversible end-organ damage. It remains unclear why Aichivirus presents a threat to B-cell deficient patients. It is possible that the lack of Aichivirus-neutralizing antibodies predisposes to chronic disseminated infection, as it is the case for enteroviruses, and that the passive protection provided by Ig substitution is insufficient. Secondary B-cell deficiency can also lead to disseminated Aichivirus infection, and it is possible that B cells play an intrinsic role beyond antibody production. In one patient with secondary B-cell immunodeficiency, B-cell restoration was associated with clearance of the virus. Nevertheless, the critical determinants of Aichivirus host defense remain to be identified. Interestingly, all four patients reported (including the two observations mentioned above) are children. It will be interesting to learn if Aichivirus poses the same threat to B-cell deficient adults.

In conclusion, we highlight human Aichivirus as a potential emerging opportunistic pathogen for patients with X-linked agammaglobulinemia and secondary B-cell deficiency, for instance, post-rituximab therapy. Potentially, Aichivirus is the underlying cause for chronic organ disease in several other conditions associated with B-cell deficiency and hypogammaglobulinemia. Progressive hepatosplenomegaly and renomegaly with infiltrating T cells appear to be indicative of Aichivirus infection. In two patients with XLA, HSCT has been associated with clearance of infection. **AQ4**

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Author Contribution

IM contributed to the concept, design, and funding and drafted the manuscript. JB and EW performed experiments. All authors edited the manuscript. IM, GB, and KJ contributed to the clinical care of the patients.

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IM is a senior clinical investigator at the Fonds Wetenschappelijk Onderzoek (FWO) Vlaanderen.

Declarations

Ethics Approval The protocol was approved as BIOKID by the Ethics Committee of the University Hospitals Leuven.

Consent to Participate The patients' parents gave written informed consent for participation and publication.

Consent for Publication The patients' parents gave written informed consent for participation and publication.

Conflict of Interest IM holds a chair in primary immunodeficiencies by CSL-Behring, paid to KU Leuven.

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