An Emerging Phenotype of Partial RAG 1/2 Deficiency Among Young Children with Autoimmunity and Viral Infections

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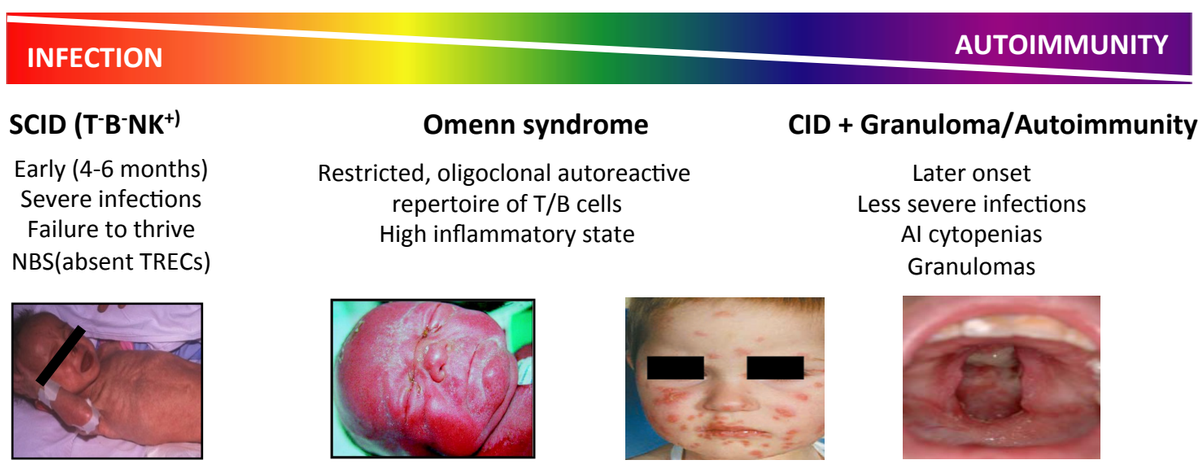
Introduction:

- RAG1 and RAG2 initiate the combinatorial joining of the VDJ gene segments that diversifies T and B cell receptor repertoire.



Functionally null *RAG1/2* mutations result in full absence of T and B cells and SCID. Partial RAG1/2 with variable recombinase activity result in a broad phenotype including CID with autoimmunity and inflammatory complications.

- Phenotypic variability of the same mutations indicates additional epigenetic factors, such as viral infections, shape the clinical presentation.
- We describe the natural history of a cohort of 12 patients with confirmed partial RAG1/2 deficiency and AI at a young age.

Objective:

Our aim was to:

- Investigate the link between viral infections and development of AI in patients with RAG 1/2 deficiency.
- Test candidate biomarkers that may reflect the underlying RAG1/2 protein deficiency.

Methods:

- Patients were enrolled through national and international collaborative effort.
- A retrospective chart review was completed.
- Autoantibody profiling was performed by microarray, Bioplex 23 and/or ELISA.

Results:

- RAG deficiency was confirmed long after onset of AI.
- *RAG1/2* mutations were fully characterized in 11 of 12 patients with average recombinase activity level ranging from 4-50%.
- Onset of viral infection ranged from 6 to 30 month of age.
- Out of 12 patients, 5 had complicated vaccine associated varicella infections, 4 had CMV infections and 2 patients had adenovirus with combination of herpes virus.
- All patient developed AI complications preceded by viral infections. Autoimmunity was mainly cytopenias including AIHA(66%), ITP (25%), and AN (25%) confirmed by serology in the majority of the cases.
- Other AI complications included severe vasculitis and thyroid disease.
- Autoantibody profiling confirmed the presence of a specific panel of anti-cytokine autoantibodies targeting IFNα, IFNω and IL-12 (8 of 9 patients tested).
- Eleven of 12 patients underwent bone marrow transplantation with high survival rate (1 of 11 deceased).

Case	Phenotype	Mutation	RAG activity	Age at Dx	Auto-antibodies
1	CID-G/AI	RAG 2	11%, 31%	Post-mortem	Direct Coombs
2	CID-G/AI	RAG 1	0.6%, 23%	20 m	Direct Coombs, IFNα
3	Leaky SCID	RAG 1	121.6%	3 y	Direct Coombs, IFNα, IFNω and IL-12
4	CID-G/AI	RAG 1	16%	-	Coombs, anti-platelet Ab
5	CID	RAG 1	41.6%, 9%	3 y	-
6	-	RAG 1	1.4%, 9.1%	2.5 Y	IFNα, IFNω and IL-12
7	-	-	-	6 y	
8	CID-G/AI	RAG 1	125.4%, 0.1%	-	IFNα, IFNω
9	CID-G/AI	RAG 2	66.3%, 30.8%	-	IFNω
10	Leaky SCID	RAG 1	1.8%	-	Direct Coombs
11	Leaky SCID	RAG 1	2.7%	-	Direct Coombs, anti-platelet antibody, IFNα, IFNω
12	Omenn	RAG 1	9.1%	-	IFNα, IFNω

Case	Vaccine	Viral Infections	Age at onset of viral infection	Auto-immunity	Age at onset of AI
1	MMRV (12 m)	VA-VZV, Rubella, Mumps	13 m	AIHA, ITP	13 m
2	MMRV (12 m)	VA-VZV	14 m	AIHA, vasculitis	16 m
3	No live MMRV	CMV, Adenovirus	14 m	AIHA, AI thyroiditis	30 m
4	No live MMRV	Varicella	6 m	AIHA, ITP	26 m
5	MMRV (Age -)	VA-VZV	24 m	AIHA, Vasculitis	2.5 y
6	VZV	VA-VZV	24 m	ITP	28 m
7	-	CMV	30 m	AIHA, AN	-
8	VZV	VA-VZV, RSV	-	AIHA, AN	-
9	VZV	VA-VZV, RSV	-	AN	-
10	-	CMV	-	AIHA	-
11	-	CMV	-	AIHA	-
12	-	Adenovirus, HHV6	-	Dermatitis	-

Conclusions:

- As an emerging new phenotype, partial RAG1/2 deficiency may present with features of complicated viral infections and autoimmunity, most commonly autoimmune cytopenias.
- A specific signature of anti-cytokine antibodies may assist the clinician to identify an underlying immunodeficiency, and initiate early definitive treatment with bone marrow transplantation.

References:

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