CEBPE Mutation Variant as a Cause of Inflammasomopathy

Bryan Witt, MD[1], Holly Miller, DO[1], Michell Lozano Chinga, MD[1]

[1]Phoenix Children's Hospital, Phoenix, AZ

Background

- *CEBPE* encodes CCAAT enhancer–binding protein epsilon (C/EBPε), an important transcription factor in the differentiation of granulocytes for which mutations primarily result in autosomal recessive neutrophil-specific granule deficiency (SGD)
- SGD is characterized by poor neutrophil chemotaxis and impaired bactericidal activity resulting in recurrent bacterial infections.
- Additional sequelae of CEBPE pathogenic variants are not widely reported in the literature.
- Currently, there is only one case study in the literature that reports *CEBPE* mutation with concomitant inflammasomopathy

Presentation

- A 6-year-old female presented for evaluation of chronic anemia and persistently elevated inflammatory markers.
- She was born at 35 weeks to non-consanguineous parents and was cyanotic at birth, but remainder of birth history is unclear.
- Early life was characterized by poor feeding, poor growth, and global developmental delay
- Infection history was remarkable for recurrent acute otitis media that improved after tympanostomy tubes, and one episode of pneumonia
- She also has a history of chronic hepatosplenomegaly and was diagnosed with autoimmune hepatitis

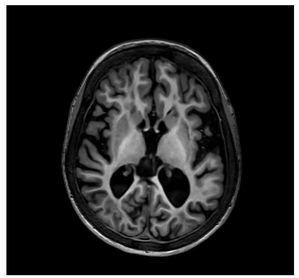
Workup (Age 6)

- Iron deficiency anemia intermixed with anemia of chronic disease, normal bone marrow, and markedly elevated ESR (57.4 mg/L and CRP (118 mm/hr)
- Cytokine panel revealed elevated IL-6, IL-8, and IL-10. Lymphocyte subsets were unremarkable
- Genetic testing revealed a heterozygous VUS in CEBPE (c.437C>T, p.Ala146Val, CADD phred: 27.5, polyphen-2: probably damaging)
- Lost to follow up prior to treatment initiation but resumed care at age 10

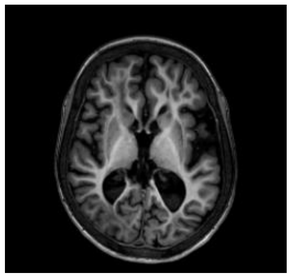
Clinical Course

	1/2024	2/2024	3/2024	4/2024	5/2024	6/2024-11/2024	12/2024	1/2025	2/2025	3/2025	4/2025
Hg (11.5-15.5 g/dL)	8.7-9.1	8.7	7.4-8.1	6.5-9.5	8.9		8.5-9.2	10.4-11.1		10.2-10.6	10.6-11.0
Ferritin (13.7-78.8 ng/mL)	100			67	145		90-144			80	
CRP (<1 mg/dL)	53-104		7.2-9.8		7.3		0.1-9.5	1.5-6.9		8.3	6.6-68.2
IgG (700-1648 mg/dL)	1907				1845		1159			606	701
Il-6 (<2.0 pg/mL)						Patient living in a different state	3.1	3.2		<2.0	
Il-8 (<3.0 pg/mL)							<3.0	4.1		<3.0	
Il-10 (<2.8 pg/mL)							45.3	96.3		51.7	
Interferon Signature	Type 1							Normal			
MOG FACS (<1:20)				Positive, 1:100				Negative			
Immunologic Interventions	Tofacitinib										
							Tocilizumab				
									Baricitinib		
									Anifrolumab		

Fig1: Table summarizing most relevant testing completed during patient's clinical course from January 2024 to April 2025. Relevant interventions are also listed with duration and temporality of treatment



(a) before tocilizumab



(b) after tocilizumab

Fig 2: MRI brain from 1/2025 during an inflammatory flare (a) and 4/2025 (b) after treatment with tocilizumab. Cortical regions showed decreased hyperintensity, consistent with improvement of inflammation

Clinical Course

- Inflammation was largely unresponsive to tofacitinib, but markers are improving with tocilizumab
- Seizures are currently managed with zonisamide, oxcarbazepine, and anifrolumab but she has continued to have breakthrough events and multiple hospital admissions for neurologic complaints
- At age 10, Interferon signature was found to be consistent with type 1 interferonopathy and MOG antibodies were positive. Both were normal at age 11 while receiving treatment with steroids, anifrolumab, and tocilizumab
- No recent infectious concerns
- Continues with recurrent flares of seizures and vision changes. Currently receiving monthly anifrolumab and baricitinib

Discussion

- To our knowledge, this is the second known instance of inflammasomopathy in the setting of a *CEBPE* mutation
- While CEBPE pathogenic variants are primarily associated with neutrophil dysfunction, features of autoinflammation can also be attributed to CEBPE gain-of-function variants
- Further investigation is needed to better characterize phenotypes of CEBPE mutations and their response to treatment

Contact

Bryan Witt
bwitt@phoenixchildrens.com