CONGENITAL, DEVELOPMENTAL AND INFLAMMATORY FINDINGS IN A PATIENT WITH A NEWLY DESCRIBED RASOPATHY (RRAS2)

Amanda Salih[1], Peter Leahy[2], Ricardo Guirola [3], Lindsay C. Burrage[4], Chao Hsiao-Tuan[5], Craigen J. William[6], Fishman S. Douglas[7], Karaviti Lefkothea[8], Jill Rosenfeld[9], Shaine A. Morris[10], Sarah K. Nicholas[11], Sarah E. Sartain[12], Manuel Silva-Carmona[13], Undiagnosed Diseases Network N/A[14], Tiphanie P. Vogel[15]

1 Baylor College of Medicine, Department of Pediatrics, Allergy and Immunology
2 Cook Children's Medical Center, Pediatrics, Genetics
3 Cook Children's Medical Center , Pediatrics, Rheumatology
4 Texas Children's/Baylor College of Medicine , Pediatrics , Department of Molecular and Human Genetics
5 Texas Children's/Baylor College of Medicine , Pediatrics, Neurology, Molecular and Human Genetics, & Neuroscience
6 Texas Children's/Baylor College of Medicine , Pediatrics, Department of Molecular and Human Genetics
7 Texas Children's/Baylor College of Medicine , Pediatrics, Gastroenterology
8 Texas Children's/Baylor College of Medicine , Pediatrics, Endocrinology
9 Baylor College of Medicine , Medicine , Department of Molecular and Human Genetics
10 Texas Children's/Baylor College of Medicine , Pediatrics, Cardiology
11 Texas Children's/Baylor College of Medicine , Pediatrics, Allergy & Immunology
12 Texas Children's/Baylor College of Medicine , Pediatrics , Hematology and Oncology
13 Texas Children's/Baylor College of Medicine , Pediatrics, Pulmonology
14 N/A, N/A, N/A
15 Texas Children's/Baylor College of Medicine , Pediatrics , Rheumatology

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Background: Germline pathogenic variants in components of the RAS-MAPK pathway have been implicated in a spectrum of developmental disorders characterized by short stature, distinct dysmorphology, and congenital heart disease collectively known as “RASopathies.” Patients with RASopathies appear at increased risk for also developing immune disorders, which may be secondary to aberrant thymic selection. Recently, activating germline mutations in RRAS2 were described as a novel RASopathy. We report a patient with a de novo RRAS2 variant and immune dysregulation.

Materials/Methods: Review of clinical history, exam findings, laboratory values, radiologic studies, pathologic studies, and deep phenotyping from expert subspecialists.

Results: A 5-year-old female presented for genetic evaluation. Her complex medical history included congenital heart disease requiring surgical interventions during infancy. Post-operatively she developed a chylothorax, and while critically ill, a pulmonary embolus and middle cerebral artery stroke resulting in symptomatic seizures. She was also noted to have imaging changes concerning for chronic lung disease. At age 3, she experienced episodes of ketotic hypoglycemia of unknown etiology. Temporally, she developed persistent fevers, serositis, polyarthritis and rash, progressing to macrophage activation syndrome; she was diagnosed with systemic juvenile arthritis. Management has been complicated by elevated aminotransferases with concerns for hepatic fibrosis by biopsy. Immune modulation controlled her hyperinflammation, but she had persistent arthritis despite intraarticular and oral corticosteroids, meloxicam, hydroxychloroquine, leflunomide, and anakinra; she is now on tofacitinib. She has not had severe, unusual or recurrent infections despite thymectomy and transient chylothorax-related

hypogammaglobulinemia. Physical exam was remarkable for dysmorphic features and arthritis. Exome sequencing revealed a likely pathogenic de novo duplication (p.Gly24_Gly26dup) in RRAS2.

Conclusions: RASopathies are characterized by classic developmental and congenital findings and increased risk for immune dysregulation. Activating RRAS2 variants were recently reported in a small number of patients. As additional patients are reported, it will become clear if concurrent immune disease is also a feature of RRAS2. This case underscores the association of RAS-MAPK activation with immune dysregulation and highlights the importance of deep phenotyping in complex patients with rare and novel disorders.

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