



Letter

Cerebral aneurysm in a 12-year-old boy with a *STAT3* mutation (hyper-IgE syndrome)

Hyper-IgE syndrome (HIES) was initially referred to as Job syndrome because patients presented with cold abscesses that resembled those found in the biblical character Job. HIES is a rare immunologic disease, with an incidence of 1 in 100,000, that affects both males and females equally.¹ Both autosomal recessive and dominant inheritance patterns have been described. The autosomal dominant HIES involves defects in the Janus activated kinase-signal transducer that lead to impaired T_H17.^{2,3} Mutations in *STAT3* have been associated with HIES.^{2,3}

STAT3, encoded on chromosome 17q21, is an important signaling molecule in immunologic responses. It provides instructions to turn genes on or off—regulating cell growth, division, movement, and apoptosis.⁴ Mutations in the *STAT3* protein, particularly in the DNA binding area, disrupt the protective immunologic process and allow for the clinically infectious phenotype.⁴

Patients with *STAT3* mutations have impaired cytokine production, leading to the formation of cold abscesses.⁴ These patients are prone to recurrent sinopulmonary infections and are also vulnerable to opportunistic infections due to their immunodeficiency.^{1–4}

Patients with *STAT3* mutations have distinct facial features that include a broad nasal base and nasal bridge, frontal bossing, wide outer canthal distances, and deep-set eyes.^{1–4} They can have various skeletal and dental abnormalities, including retention of natal teeth, scoliosis, osteoporosis, and bone fractures. Patients may be at an increased risk of lymphoma and neurologic and vascular abnormalities.^{5,6}

Vascular aneurysms have recently been described as part of the HIES spectrum, including both *STAT3* mutations and *DOCK8* mutations.^{5,6} One case of HIES with a cerebral aneurysm has already been described in a pediatric patient, which involved a *DOCK8* mutation. Our case represents the first report, to our knowledge, of a cerebral aneurysm in a pediatric patient with a *STAT3* mutation.

A 12-year-old boy was diagnosed as having a *STAT3* mutation near birth, specifically located in the SH2 domain (V637M).⁷ At 18 months of age, his IgE level was 400 IU, and a level checked before this was 259 IU. The patient had a strong positive family history of *STAT3* mutations, including his father and 2 siblings. The father and affected siblings did not have any known vascular abnormalities, but they had recurrent infections and were receiving intravenous immunoglobulin treatment. The one sibling also had retention of her natal teeth.

The patient's medical history included frequent ear infections and mastoiditis that required drilling and sealing off mastoid air cells. At 3 years of age, he was diagnosed as having a right internal carotid artery pseudoaneurysm that was 1.1 × 1.0 cm in the petrous segment. Subsequent head imaging did not reveal any increase in size or changes in the pseudoaneurysm.

At 12 years of age, the patient noted an increase in headaches and diplopia that worsened with exertion. Magnetic resonance imaging (MRI) revealed an enlarged right carotid artery aneurysm. A cerebral angiogram with balloon test occlusion identified a 2.5 × 2.4-cm right internal carotid artery petrous segment aneurysm with a wide neck. The patient underwent a successful surgical ligation of the right internal carotid artery with prophylactic treatment of vancomycin because of a history of methicillin-resistant *Staphylococcus aureus* colonization (Fig 1). No coiling was done because this increased risk of infection with foreign material in the body. The patient's headaches and diplopia slowly improved after the surgery.

STAT3 mutation is a rare immunologic disease that clinically manifests with elevated IgE level, connective tissue, skeletal system, and dental and vascular abnormalities.^{1–4} These vascular abnormalities have been reported in the brain, lung, aorta, heart, veins, skin, and foot.^{5,6} A study performed by Chandresis et al⁵ investigated 21 adults with *STAT3* mutation for vascular abnormalities. They found that 95% of patients had some brain abnormalities, 85% had brain artery abnormalities, and 50% had coronary artery abnormalities.

Although cerebral aneurysms have been described in the adult patients with *STAT3*, no pediatric patients with the *STAT3* mutation have been identified as having such abnormalities.^{5,6} This is the first reported case, to our knowledge, of an intracranial aneurysm in a

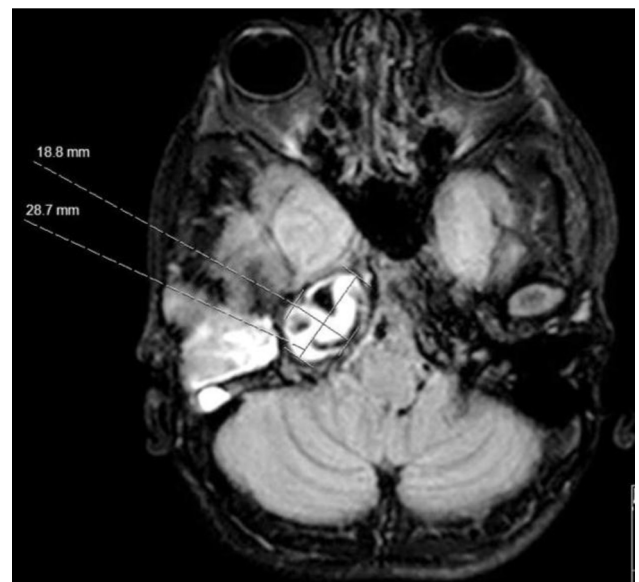


Figure 1. T2-weighted fluid-attenuated inversion recovery magnetic resonance image.

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.jana.2015.02.016>

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pediatric patient with a *STAT3* mutation. The mechanism of why these patients are prone to vascular complications is not completely understood. A review by Yavuz and Chee⁸ discusses several possible pathogenetic mechanisms. They suggest that eosinophilia, infection, and genetics all may play a role in the development of vascular complications. Despite the propensities for vascular abnormalities, neither adult nor pediatric populations with *STAT3* mutations are routinely screened for brain abnormalities with MRI.

A study performed by Freeman et al⁶ documented the increased incidence of brain abnormalities found in patients with HIES compared with the general population. Screening cerebral MRI may lead to the prevention of life-threatening complications in the HIES patient population. Our case study additionally suggests that cerebral MRI screening in the pediatric population with *STAT3* mutation may result in a decrease in cerebral incidents as these patients enter adulthood. When making this suggestion, it is important to consider both the potential risks and benefits. The MRI itself proposes few risks because it is noninvasive and does not expose the patient to radiation. The scan can be time-consuming and may be uncomfortable for the child. Cost may be the biggest deterrent. The price of a brain MRI can range from \$600 to \$1000.⁹ Even though the screening MRI may be time-consuming and expensive, the potential benefits outweigh the disadvantages. Any vascular anomalies will be detected, patients can be followed over time, and the appropriate interventions can be taken. Therefore, a screening brain MRI should be part of the comprehensive management program for pediatric patients with HIES.

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