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A type I interferon signature identifies bilateral striatal necrosis due to mutations in ADAR1.

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Abstract

BACKGROUND:

We recently observed mutations in ADAR1 to cause a phenotype of bilateral striatal necrosis (BSN) in a child with the type I interferonopathy Aicardi-Goutières syndrome (AGS). We therefore decided to screen patients with apparently non-syndromic BSN for ADAR1 mutations, and for an upregulation of interferon-stimulated genes (ISGs).

METHODS:

We performed Sanger sequencing of ADAR1 in a series of patients with BSN presenting to us during our routine clinical practice. We then undertook detailed clinical and neuroradiological phenotyping in nine mutation-positive children. We also measured the expression of ISGs in peripheral blood from these patients, and in children with BSN who did not have ADAR1 mutations.

RESULTS:

Nine ADAR1 mutation-positive patients from seven families demonstrated an acute (five cases) or subacute (four cases) onset of refractory, four-limb dystonia starting between 8 months and 5 years of age. Eight patients were developmentally normal at initial presentation. In seven cases, the disease was inherited as an autosomal recessive trait, while two related patients were found to have a heterozygous (dominant) ADAR1 mutation. All seven mutation-positive patients assayed showed an upregulation of ISGs (median: 12.50, IQR: 6.43-36.36) compared to controls (median: 0.93, IQR: 0.57-1.30), a so-called interferon signature, present many years after disease onset. No interferon signature was present in four children with BSN negative for mutations in ADAR1 (median: 0.63, IQR: 0.47-1.10).

CONCLUSIONS:

ADAR1-related disease should be considered in the differential diagnosis of apparently non-syndromic BSN with severe dystonia of varying evolution. The finding of an interferon signature provides a useful screening test for the presence of ADAR1 mutations in this context, and may suggest novel treatment approaches.

KEYWORDS:

Clinical genetics, Immunology (including allergy), Molecular genetics, Neurology

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