LETTER

Cerebral vasculopathy is a common feature in Aicardi–Goutières syndrome associated with *SAMHD1* mutations

In their recent interesting paper, Xin et al. (1) described an autosomal recessive condition in 14 individuals of Old Order Amish ancestry characterized by cerebral vasculopathy and early onset stroke. The affected patients presented a heterogeneous phenotype, including variable developmental disability, irritability in infancy, chilblain lesions, glaucoma, and arthritis. Through genome-wide homozygosity mapping and candidate gene sequencing, the authors identified the homozygous mutation c.1411-2A > G in *SAMHD1* being associated with this entity. Additionally, they detected this mutation in 3 of 44 patients with developmental delay (phenotypes not further described). Although mutations in *SAMHD1* have been found to be disease-causing in Aicardi–Goutières syndrome (AGS) (2), Xin et al. (1) stated that "the phenotype reported here is apparently incompatible with Aicardi–Goutières syndrome" and that "none of our 17 patients has been diagnosed with Aicardi–Goutières syndrome."

Although, as Xin et al. (1) explained, AGS is most commonly recognized as "a type of encephalopathy whose clinical features mimic those of acquired in utero viral infection," there now exists an extensive literature highlighting the diverse spectrum of phenotypes that can occur in the context of AGS (an overview is provided in ref. 3). Thus, for example, neurological dysfunction in AGS is not always progressive or, indeed, necessarily present at all; microcephaly is not always seen; onset is not always in the first year of life; intracranial calcification and white matter changes are not inevitable; and a cerebrospinal fluid (CSF) lymphocytosis is absent in a considerable number of affected individuals. We accept that such diversity makes clinical diagnosis challenging. However, we consider that the clinical findings presented by Xin et al. (1), most particularly the chilblain lesions, early irritability, and glaucoma, should prompt consideration of the diagnosis. We suggest that it might be sensible for Xin et al. (1) to confirm that intracerebral calcifications were not evident on computed tomography and that reliable CSF indices (elevated white cells and increased titers of IFN-α and pterins) of AGS were not present in any of their cases (with recognition of the age-dependent nature of the CSF findings).

Irrespective of diagnostic classification, there are two earlier independent descriptions of cerebral arterial stenoses, stroke, and cerebral vasculopathy in patients with AGS carrying mutations in *SAMHD1* (4, 5). These two papers fully encompass the phenotypes described in the article by Xin et al. (1). In our view, recognizing that the Old Order Amish disorder is part of the AGS-related phenotype means that future understanding of AGS disease pathogenesis will have relevance to the Amish community also.

In summary, we would argue that Xin et al. (1) did not present a new clinical condition but described a heterogeneous group of Old Order Amish individuals with AGS and intracerebral arteriopathy. Based on our previous work and their findings, we conclude that intracerebral large artery disease is a common phenomenon in patients with *SAMHD1* mutations. Interestingly, we have never observed large artery disease in association with mutations in *TREX1, RNASEH2A, RNASEH2B,* or *RNASEH2C*, perhaps indicating a particular role for SAMHD1 in blood vessel integrity and homeostasis.

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