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LETTER TO EDITOR

RNASEH2B Related Adult-Onset Interferonopathy

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To the Editor,

At least 18 different single-gene disorders have been described associated with elevated levels of type I interferon. These "type I interferonopathies" typically result in severe pediatric disorders, including STING-associated vasculopathy of infancy (SAVI) caused by gain of function mutations in *TMEM173*, spondyloenchondropdysplasia (SPENCD) caused by biallelic *ACP5* mutations, and Aicardi-Goutières syndrome (AGS) caused by mutations in one of seven different genes: *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *ADAR1*, *SAMHD1*, or *IFIH1* [1]. AGS is the most commonly recognized interferonopathy and in over 90% of cases presents within the first year of life with neurological impairment associated with intracranial calcification and leukodystrophy, and in around a third of cases acral chilblains develop [2]. The type I interferonopathies occur due to aberrant metabolism of nucleic acids/dysregulation of the interferon pathway, resulting in induction of type I interferon and interferon-stimulated genes (ISGs). Serum interferon alpha or whole blood ISGs can be measured and the observation of persistently elevated levels assists diagnosis [3].

RNASEH2A, *RNASEH2B*, and *RNASEH2C* encode the three subunits of the ribonuclease H2 enzyme, which cleaves the RNA strand of RNA/DNA heteroduplexes. Biallelic mutations in any of these three genes result in impaired ribonucleotide removal with enhanced type I interferon production. *RNASEH2B* is the commonest disease-causing gene in AGS (36%). *RNASEH2B* may be associated with a milder clinical phenotype than the other recognized AGS genes, with around 1 of 20 cases presenting with an isolated spastic paraparesis and normal intellect. Despite the recognized milder phenotype, to date, all patients with biallelic mutations described have presented with a pediatric-onset disease with clinically discernable neurological manifestations. In a cohort of 107 families with *RNASEH2B* mutations, 97 harbored a recurrent p.Ala177Thr substitution (48 homozygotes, 49 heterozygotes) [2]. This mutation affects a highly conserved amino acid and functional studies have demonstrated protein destabilization [4].

We report a 32-year-old female of Indian origin, born to non-consanguineous parents. She reports a healthy childhood with no additional support required in education, which was completed at 15 years of age. She describes however, that shortly after moving to the UK, at age 19 years she developed cold-exacerbated purple discoloration of the skin and ulcerations at the dorsal and volar aspects of the finger and toes. Three episodes of severe digital ischemia over this 13-year period had required admission for iloprost infusions. Regular sildenafil and amlodipine were prescribed, although dose adjustment was required due to syncopal events.

She reported a history of depression and mood swings, early-morning joint stiffness and generalized muscular pain consistent with fibromyalgia, intermittent dry eyes, hair loss, and a constantly dry mouth. These symptoms, combined with childcare responsibilities, have prevented her from working. Over a 4-year period, from the age of 26 years, ten teeth in the lower left quadrant and molar and premolars in the upper right quadrant were removed. Dental review at age 31 years concluded that the dental loss was most likely due to decay. There was no history of learning difficulties, seizures, dystonia, or hypothyroidism. Ophthalmic review at age 31 years demonstrated equal pressure in both eyes. It was noted that the left eye's cup:disc ratio was larger than the right eye's, though still

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within the normal limits. At follow-up 12 months later, ophthalmic pressures remained normal.

There was no family history of neurological disease, chilblains, or dental loss. The proband had a 14-year-old child who was healthy, while the mother of the proband had psoriasis.

On examination, there was tapering of the left 5th digit, and erythematous lesions and scaling of the fingers and the dorsal aspects of the toes (Fig. 1a). There was erythematous dry skin at the angle of the jaw bilaterally. Head circumference was 54 cm (mean size for an adult female), and cardiorespiratory and abdominal examination was unremarkable. Neurological examination demonstrated normal gait, tone, and reflexes; muscle strength assessment was pain inhibited; and there were 10 tender points of fibromyalgia. The absence of teeth in the lower left and upper right quadrants was noted.

Full blood count was normal and erythrocyte sedimentation rate was 21 mm/h (0 to 27). Autoantibody screen was negative. X-Rays showed acro-osteolysis of the 2nd and 3rd toes bilaterally (Fig. 1b). Nailfold capillaroscopy was not suggestive of an underlying systemic sclerosis spectrum disorder (only some slightly dilated capillary loops in one finger). Cranial imaging was declined.

With research consent (REC reference 17/SC/0026), ISGs were assayed by qPCR of whole blood RNA, per previously detailed methods [3], and an elevated ISG score was detected on three separate occasions over a 2-year period. The elevated ISG score was comparable with that observed in a cohort of pediatric patients with a clinical and molecular diagnosis of AGS and was significantly higher than that in a control cohort ($p = 0.022$) (Fig. 1c). Genetic testing on a targeted gene panel identified a homozygous c.529G>A; p.(Ala177Thr) *RNASEH2B* mutation. As noted above, this is the most frequently observed pathogenic mutation in *RNASEH2B* [2, 4]. Previously, we have described 46 patients from 44 families with this specific homozygous genotype. Forty-two had a clinical diagnosis of AGS and 4 of spastic paraparesis. The ISG score, measured at ages ranging from 0.34 to 19.07 years, was elevated (> 2.466) in 48 of 71 assays undertaken in this cohort (ranging from just above normal range to 61.74) and was within normal range on 23 assays. Thus, our patient's scores of 8.805, 6.669, and 11.259 are well within the recognized range of pathogenic *RNASEH2B* mutations. The value of the ISG score itself is known to fluctuate over time within an individual, but it is of interest that a clinical phenotype

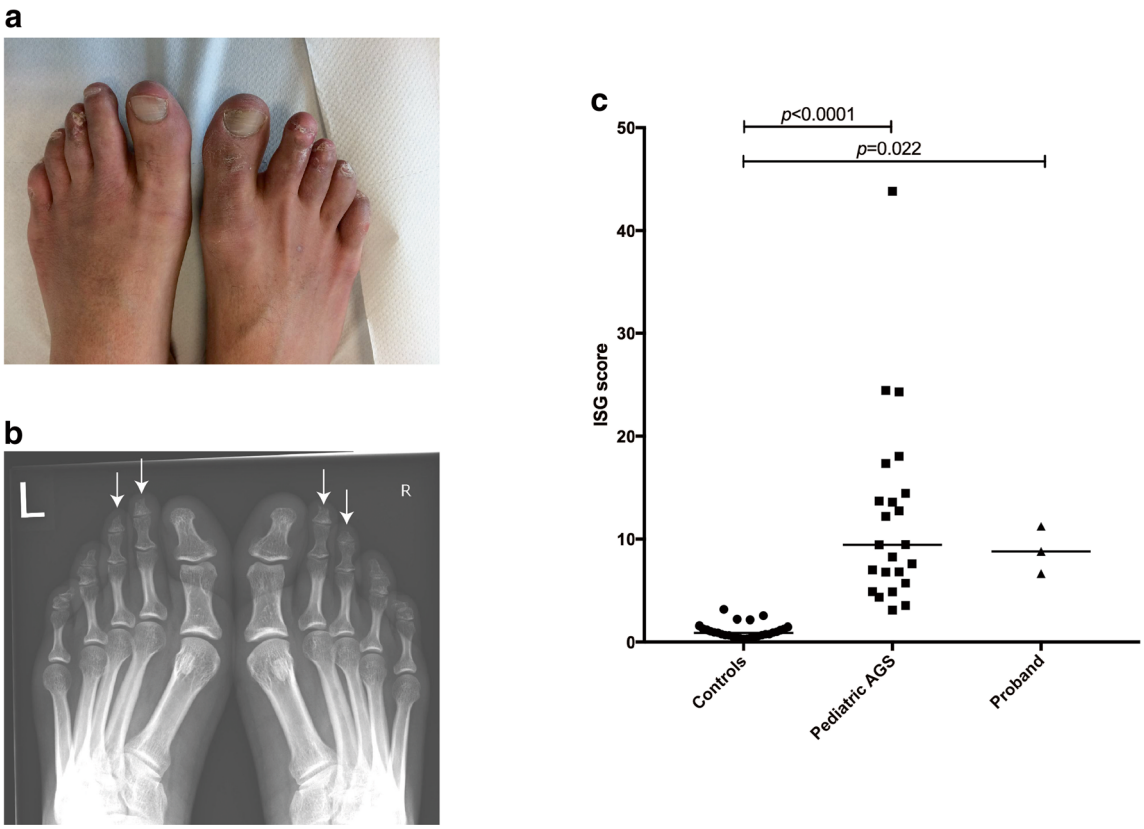

Fig. 1 Digital manifestations and type I interferon elevation associated with a biallelic *RNASEH2B* mutation. Erythema and scaling of the toes (**a**) with associated underlying acro-osteolysis of the 2nd and 3rd toes bilaterally on X-ray (**b**) is observed (see arrows). Whole blood qPCR assessment of six ISGs was undertaken to derive an ISG score, which was elevated on three occasions 12 months apart and was comparable to that observed in pediatric cases of confirmed AGS due to *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *ADAR1*, *SAMHD1*, or *IFIH1* and was significantly higher than in healthy controls (**c**)

without an elevated interferon score is a finding noted in *RNASEH2B* more than the other known AGS-associated genes, the reason for which is not clear [5].

Heterozygous mutations in *TREX1* [2], *SAMHD1*, and *TMEM173* have previously been associated with chilblain lupus. Furthermore, systemic lupus has been associated with heterozygous mutations in known "interferonopathy" genes, including *TREX1*, *ACP5*, and the *RNASEH2* complex [6]. However, in this case, we observe the same recurrent biallelic *RNASEH2B* mutation previously associated with pediatric neurological and skin disease [2] in adulthood. In the absence of imaging, the presence of intracranial calcification or white matter abnormalities cannot be excluded in our case. However, the late onset of digital ischemia and the absence of neurological manifestations on clinical examination are of particular note; the reason for this clinical variability is not currently clear but may relate to as yet undefined modifier genes, epigenetic factors, or potential environmental factors differentially triggering nucleic acid metabolism.

We note the discrepant left eye's cup:disc ratio and, given the known association of glaucoma associated with IFN-driven disorders such as AGS and Singleton-Merten syndrome [2, 6, 7], we intend to continue to review this annually as recommended in AGS [2]. We also note the early loss of secondary dentition and speculate that this may also relate to the underlying genetic disorder, given the well-described association of dental anomalies (early-onset periodontitis and root resorption) in IFIH1-associated disease [7, 8].

This case highlights the need to consider monogenic causes of acral cyanosis, particularly in patients with severe skin disease, a significant family history, and additional neurological, dental, or perhaps ophthalmic manifestations.

Given the development of JAK-STAT inhibitors and anti-interferon antibodies, identifying the underlying molecular etiology of severe digital ischemia gives real promise of a targeted therapy.

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Compliance with Ethical Standards

With research consent (REC reference 17/SC/0026). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Key message Type I interferonopathies, including *RNASEH2B* mutations, should be considered in adults with severe digital ischemia.

Conflict of Interest The authors declare that they have no conflict of interest.

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