HOT TOPIC

Reduced Penetrance in Interferonopathy-Associated Dystonia: Hope for Clues to Mechanism?

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Type-I interferons (IFNs) are crucial regulators of inflammation, exerting pleiotropic functions during infections.[1] Overproduction of type-I IFNs, as seen in interferonopathies, has detrimental effects on nervous-system integrity. Moreover, neurotoxicity of excessive type-I INF levels has been implicated in autoinflammatory and autoimmune processes related to diverse brain diseases, including neuropsychiatric systemic lupus erythematosus, HIV-associated neurocognitive disorders, and chronic neurodegenerative conditions (eg, Parkinson's disease, Alzheimer's disease).[1]

A prototype of type-I interferonopathies is Aicardi-Goutières syndrome (AGS), encompassing a group of heterogeneous conditions in which dystonia can be the leading clinical sign.[1] By conducting a seminal study of causally unexplained phenotypes linked to upregulated type-I IFNs, Zhu and colleagues[2] were able to expand the spectrum of monogenic interferonopathies with dystonic features. The researchers identified 12 affected individuals who displayed highly similar presentations of inflammatory encephalopathy characterized by dystonia, spasticity, and loss of acquired language. All patients were found to carry heterozygous loss-of-function variants in the previously unassigned disease-gene *PTPN1*, encoding an essential tyrosine-protein phosphatase (PTP1B) that influences immune reactions.

The mutations, which were shown to result in reduced *PTPN1* expression consistent with haploinsufficiency, produced abnormal activation of type-I IFN-stimulated genes in blood and defects in INF signaling in patient-derived fibroblasts. Six patients showed response to immunotherapy, suggesting that *PTPN1* variants may represent an under-diagnosed cause of treatable movement disorders.[2] Intriguingly, inheritance of the disease-associated *PTPN1* allele from an asymptomatic parent was observed in eight families (73%).[2]

Non-manifestation in the context of pathogenic variants has also been reported for dystonic forms of AGS, such as *ADAR1*-, *IFIH1*-, and *RNASEH2B*-related diseases.[1] Moreover, PTP1B is a key component of the integrated-stress-response (ISR), a unifying molecular pathway in dystonia in which several effectors have been demonstrated to cause incompletely penetrant dystonic symptoms.[3] Although no clear trigger of disease-onset was described for the majority of patients from Zhu and colleagues, four subjects had fever around the time of initial presentation.[2] Similarly, an association between febrile illness and symptom manifestation and/or deterioration is increasingly recognized for AGS[4] and ISR-linked monogenic syndromes with dystonia, including those caused by mutations in *EIF2AK2* and *PRKRA*.[3]

An elucidation of the relevant environmental exposures and/or immunopathogenic influences could provide much-needed insights into the contributors of (non-)penetrance in interferonopathy-related dystonia. More broadly, immunological factors underlying pathogenesis are emerging as an important area of investigation in isolated dystonia.[5] For example, aberrant INF levels were detected in a recent proteomics screening in adult-onset dystonia.[5] Given that extreme phenotypes can help to understand mechanisms of more common disease subtypes, we should consider that knowledge about gene–environment interactions in rare inborn errors of immunity may inform biomarker discovery

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and therapeutic strategies in the broader dystonia population.

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