GeNeDit

Think of Rare Commonly!

Editorial

Monogenic diseases are rare! But presentations of many of them overlap with, or are similar to those of common non-genetic or multifactorial disorders. Studies on novel genes of autoinflammatory disorders described in the GenExpress in this issue highlight the same point. These papers talk about gain-of-function mutations in genes involved in innate immunity. The presenting features of these monogenic autoinflammatory disorders are fever and '–itis', associated with haematological markers of inflammation; the features are similar to those of infections or autoimmune disorders. Recurrent episodes in the absence of immunodeficiency make one suspect that these can be autoimmune disorders. More than 100 autoimmune disorders are delineated, many of them with overlapping features. Development of the speciality of clinical immunology and expert management by the specialists has improved the outcomes of autoimmune disorders. But rarely the auto-antibodies are conspicuous by their absence in clinically suspected autoimmune disorders and in such scenarios, testing of multiple genes in one go clinches the diagnosis of monogenic auto-inflammatory disorders.

Autoinflammatory and autoimmune disorders are inflammatory disorders due to defects in the immune system. The autoinflammatory disorders are due to defects in the genes involved in innate immunity and its pathways. The inflammation starts by itself without known external triggers like microorganisms. On the other hand, autoimmune disorders are due to abnormalities of adaptive immunity where the body mistakes a cell type that is actually "self" as "other". These are akin to 'learning mistakes', while in autoinflammatory disorders the 'mistakes are in the basic knowledge' of the immune competent cells. As mentioned previously, the resulting symptoms are very similar. Presence of family history or consanguinity can help in clinical suspicion in addition to documented absence of autoantibodies. Some autoimmune disorders also have family history of other autoimmune disorders as they also have multifactorial etiology which includes a genetic component. Some autoinflammatory disorders manifest during fetal life or infancy and have overlapping features with infective disorders. This group includes pseudo-TORCH syndrome and Aicardi-Goutieres syndrome for which 3 and 9 causative genes are known till date. Correct diagnosis is important not only for appropriate management but also for genetic counseling as there may be 25 or 50% risk of recurrence in the family members. For severe disorders with early lethality and neurological involvement, the option of prenatal diagnosis also may be useful for the families. Specific targeted therapies also may become available as the genetic diagnosis provides knowledge of the molecular pathways involved in disease pathogenesis.

The monogenic autoinflammatory disorders should open our minds to rare monogenic causes of common presentations and stress the need for considering these etiologies in common presentations. Similar overlap is seen in other diseases with heterogeneous etiologies like diabetes mellitus, nephrotic syndrome, cardiomyopathy, hypertension, cataract, etc. In fact, there are monogenic causes for each of these clinical conditions, even though more often they are associated with multifactorial etiology. Understanding the genetics of rare monogenic disorders also paves the way for obtaining insights into the pathogenesis of common multifactorial disorders, which in turn helps in identifying therapeutic targets for novel drug development. It is thought that the genetic variants in the genes for monogenic disorders may be contributing as susceptibility loci for common multifactorial disorders.

Don't think of rare diseases rarely if you don't want to miss any diagnosis!

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1st October, 2021