Mutant Adenosine Deaminase 2 in a Polyarteritis Nodosa Vasculopathy

Abstract:
Background
Polyarteritis nodosa is a systemic necrotizing vasculitis with a pathogenesis that is poorly understood. We identified six families with multiple cases of systemic and cutaneous polyarteritis nodosa, consistent with autosomal recessive inheritance. In most cases, onset of the disease occurred during childhood. Methods
We carried out exome sequencing in persons from multiply affected families of Georgian Jewish or German ancestry. We performed targeted sequencing in additional family members and in unrelated affected persons, 3 of Georgian Jewish ancestry and 14 of Turkish ancestry. Mutations were assessed by testing their effect on enzymatic activity in serum specimens from patients, analysis of protein structure, expression in mammalian cells, and biophysical analysis of purified protein. Results
In all the families, vasculitis was caused by recessive mutations in CECR1, the gene encoding adenosine deaminase 2 (ADA2). All the Georgian Jewish patients were homozygous for a mutation encoding a Gly47Arg substitution, the German patients were
compound heterozygous for Arg169Gln and Pro251Leu mutations, and one Turkish patient was
compound heterozygous for Gly47Val and Trp264Ser mutations. In the endogamous Georgian
Jewish population, the Gly47Arg carrier frequency was 0.102, which is consistent with the high
prevalence of disease. The other mutations either were found in only one family member or patient or
were extremely rare. ADA2 activity was significantly reduced in serum specimens from patients.
Expression in human embryonic kidney 293T cells revealed low amounts of mutant secreted protein.

Conclusions
Recessive loss-of-function mutations of ADA2, a growth factor that is the major
extracellular adenosine deaminase, can cause polyarteritis nodosa vasculopathy with highly varied
clinical expression. (Funded by the Shaare Zedek Medical Center and others.) Adenosine deaminase
2 (ADA2) is a protein with at least two functions. It is a growth factor affecting leukocytes and
endothelial cells and an enzyme that influences purine metabolism. This study shows that mutant
ADA2 causes polyarteritis nodosa. Polyarteritis nodosa, first described in 1866,(1) is a systemic
necrotizing vasculitis that affects medium and small muscular arteries.(2),(3) The ensuing tissue
ischemia can affect any organ, including the skin, musculoskeletal system, kidneys, gastrointestinal
tract, and the cardiovascular and nervous systems. Polyarteritis nodosa is usually diagnosed in
middle age or later but can appear in childhood.(2),(4),(5) The diagnosis remains challenging despite
classification criteria for adults(6) and children,(7) because polyarteritis nodosa frequently presents
with nonspecific constitutional symptoms, and organ involvement and disease severity are highly
varied. Polyarteritis nodosa is most often primary, but in adults it may be associated ...

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