Infantile neuroaxonal dystrophy and pantothenate kinase-associated neurodegeneration

Locus heterogeneity

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Abstract—Common clinical, radiologic, and pathologic features in infantile neuroaxonal dystrophy (INAD) and pantothenate kinase-associated neurodegeneration (PKAN) have led to the hypothesis of an allelic relationship. With the discovery of the gene defect in PKAN, this can now be tested directly. The authors excluded linkage in one consanguineous INAD family by haplotype analysis. Moreover, sequencing in seven INAD families revealed no mutations in PANK2 or in other genes of CoA biogenesis. Thus, INAD and PKAN are genetically heterogeneous disorders.

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Infantile neuroaxonal dystrophy (INAD, OMIM #256600) and Hallervorden-Spatz syndrome (HSS, OMIM #234200) have several features in common. In particular, pathologic examination shows widespread axonal swelling and spheroid bodies in the CNS in both diseases. Since the first description of INAD,1 there has been discussion whether these syndromes are distinct entities or manifestations of a continuum. Recently, mutations in the gene for pantothenate kinase 2 (PANK2) were identified as the genetic cause in the majority of typical HSS patients,2 now referred to as pantothenate kinase-associated neurodegeneration (PKAN). Mutations in the same gene were also found in the clinically similar HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration, OMIM #200150).3 To determine if INAD and PKAN share a common genetic etiology, we performed haplotype analysis and mutation screening in seven INAD families.

Patients and methods. Patients. We investigated eight INAD patients from seven previously described4–3 families. INAD was confirmed pathologically in skin biopsies of all index patients. On MRI two affected brothers (family INAD3) showed the eye-of-the-tiger sign characteristic of PKAN.4 Informed consent was obtained from all participants.

Haplotype analysis. Marker alleles (D20S193, D20S889, RH29130, GATA149E11) were PCR-amplified using fluorochrome-labeled primers, analyzed using a capillary sequencer, and evaluated with GeneScan software version 4.0 (Applied Biosystems).

Results. Families INAD1–3 were genotyped for up to four polymorphic microsatellite markers covering a region of 600 kb each on both sides of PANK2. Within this interval the probability of double recombination should be <1:10,000. We detected at least one fully informative marker on both sides of PANK2 for each family and no evidence for recombination in the analyzed interval (figure).

In families INAD1 and INAD2, haplotypes of affecteds were different from those of non-affecteds. These findings neither exclude nor confirm linkage to PANK2, but are likely to be mere chance. In the consanguineous family INAD3, haplotyping showed no common allele in the parents and discordance between the two affected siblings. In an autosomal recessive trait both findings argue against linkage to the PANK2 locus. Using markers D20S193, D20S889, and an intragenic SNP, the multipoint lod score

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(allele frequency 0.01, penetrances: 0.001, 0.001, 1.0) was <-2 across the entire region.

Heterogeneity in INAD could lead to these results without precluding PANK2 as a candidate gene. Therefore, we performed mutation screening and found no mutations in any of the eight patients from seven families. To exclude deletions or duplications, we performed quantitative PCR and did not observe amplification below or above the values expected for biallelic presence (RQ value of 1.0 ± 0.2) of each exon. In summary, we did not detect PANK2 mutations or large deletions/duplications in any of the eight patients. Since the downstream enzymes of PANK2 in the CoA biosynthesis pathway represent the most obvious additional candidate genes, we chose to screen the entire coding regions of the corresponding genes. However, in none of these genes did we detect mutations in the eight INAD patients.

Discussion. In order to avoid the eponym HSS (given the unethical activities of Julius Hallervorden during the Third Reich), the use of the term PKAN is encouraged for patients with PANK2 mutations, while HSS patients without mutations may be classified within the group of disorders called neurodegeneration with brain iron accumulation (NBIA). In this article, we have retained the designation HSS when necessary, e.g., to discuss the neuropathologic issues that were historically documented in HSS patients.

Both INAD and HSS are young-onset neurodegenerative disorders that are inherited as autosomal recessive traits. They differ, however, with respect to their course and clinical phenomenology. While INAD usually starts within the first 2 years of life and leads to death before age 10, HSS has a late-infantile or juvenile onset and patients may survive into their third decade. INAD is characterized by a mainly pyramidal syndrome with spastic tetraplegia and hyperreflexia, along with progressive psychomotor regression, visual impairment, and dementia. HSS, on the other hand, is an extrapyramidal syndrome with dystonia, parkinsonism, and choreoathetosis, and it may be accompanied by a pyramidal syndrome and dementia. Differential diagnosis is, however, hampered by the fact that there are early-infantile cases of HSS as well as late-onset cases of INAD. Similarly, there may be considerable overlap in the clinical symptoms.

Most of the debate whether INAD and HSS are distinct entities or manifestations of a continuum comes, however, from neuropathology. One of the principal histologic features in both disorders is the widespread occurrence of axonal swellings and spheroid bodies throughout the CNS. This dystrophy of neuronal axons was eponymous for INAD, but is also obligatory, even though less marked, in HSS. Iron accumulation leading to a rust-brown discoloration of globus pallidus and substantia nigra is the pathologic hallmark of HSS. These pigment deposits are absent in many cases of INAD, but transitional forms have been described with some degree of iron accumulation in the basal ganglia. This overlap prompted Seitelberger to consider his cases of INAD as infantile forms of HSS, while others referred to HSS as a juvenile neuroaxonal dystrophy. Several authors suggested that INAD and HSS are at the extremes of a disease spectrum with INAD being characterized by widespread spheroid bodies throughout the CNS without excessive pigment in the basal ganglia, and HSS by more localized axonal dystrophy and predominant pigment accumulation in the basal ganglia.

There is, however, a possibility for pathologic discrimination in vivo, as in INAD, but not in HSS, dystrophic axons are also found in distal peripheral nerves. The latter finding may bring about another differential diagnosis, giant axonal neuropathy (GAN, OMIM #256850). GAN is an autosomal recessive neurodegenerative disorder of early onset, caused by mutations in the gigaxonin gene. In contrast to INAD and HSS, there is a prominent neuropathy in addition to CNS signs. The hallmark of the disease is giant axonal swellings due to a massive accumulation of neurofilaments in peripheral nerves that can normally be differentiated from the dystrophic axons in INAD.

Neuroimaging may also contribute to the differential diagnosis. MRI in INAD shows cerebellar atrophy often associated with hyperintensity in the cerebellar
The classic MRI feature of HSS is a hyperintensity within a region of hypointensity in the medial globus pallidus on T2-weighted images, a pattern known as “eye of the tiger.” In a large series, all of 69 patients with PANK2 mutations had this sign, while all of 16 mutation-negative patients showed only hypointensity in the globus pallidus without central hyperintensity. Therefore, it has been proposed that there is a one-to-one correlation between the eye-of-the-tiger sign and mutations in PANK2. However, reflecting the clinical and pathologic overlap between INAD and PKAN, we found an eye of the tiger in the two affected brothers of family INAD3. Thus, this MRI feature is not specific to patients with mutations in PANK2, but may also be found in INAD.

Taken together, there is clinical, radiologic, and pathologic overlap between INAD and PKAN. Our data, however, provide strong evidence that INAD is not allelic to PKAN, but that these syndromes are genetically heterogeneous. Moreover, we found no evidence that INAD may be due to defects in other genes of the coenzyme A biosynthesis pathway. Although we did not search for mutations in noncoding regions of these genes, we consider it unlikely that such mutations would occur exclusively in seven unrelated patients.

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