Infantile Neuroaxonal Dystrophy

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Abstract

Infantile neuroaxonal dystrophy (INAD) is a rare autosomal recessive neurodegenerative disorder with onset in the first or second year of life. Frequency is unknown. It is characterized by a progressive motor and mental deterioration, bilateral pyramidal tract signs, marked hypotonia and early visual disturbances without epileptic seizures. The pathological hallmark of the disease is the presence of axonal swellings and "spheroid bodies" throughout central and peripheral system, evidenced by skin, nerve, conjunctiva, and rectum biopsy. Electrophysiological and radiological studies may be helpful for the diagnosis, which is based on the combination of clinical and pathological aspects. The basic metabolic and genetic defect is unknown and currently no effective treatment is available. Management includes physiotherapy and symptomatic treatment of spasticity.

Keywords

Infantile neuroaxonal dystrophy, spheroid bodies, neurodegeneration with brain iron accumulation (NBIA), Hallervorden-Spatz syndrome, neurodegenerescence

Disease names and synonyms
Infantile neuroaxonal dystrophy (INAD), Seitelberger disease

Definition/Diagnostic criteria
Infantile neuroaxonal dystrophy (INAD, OMIM 256600) or Seitelberger disease is a rare neurodegenerative disorder inherited as an autosomal recessive trait, with onset in the first or second year of life (Aicardi *et al.*, 1979; Jellinger, 1973). The clinical picture is characterized by psychomotor regression and hypotonia, which progress to spastic tetraplegia, visual impairment and dementia (Aicardi *et al.*, 1979). The diagnostic criteria for INAD have been defined as followed: onset of symptoms before 3 years of age; a clinical picture characterized by psychomotor degeneration, increasing neurologic involvement with symmetric pyramidal tract signs and marked truncal hypotonia; a relentlessly progressive course leading to spastic tetraplegia, blindness and dementia, and unequivocal histological evidence (Aicardi *et al.*, 1979).

Differential diagnosis

The constellation of clinical, neurophysiological and MRI abnormalities makes the differential diagnosis of the disease from other known degenerative disorders in the same age range relatively easy. Metachromatic leucodystrophy and various types of gangliosidosis, in particular the late form of GM1 gangliosidosis can be ruled out by the normal nerve conduction velocities and enzymatic studies in leukocytes or fibroblasts. The absence of seizures and myoclonus, the normal electroretinogram and the different EEG abnormalities make the distinction between INAD and ceroid-lipofuscinosis easy. The MRI and neurophysiological abnormalities may help distinguishing INAD from Leigh's subacute and other encephalomyelopathies and static conditions, since the progression of INAD may be very slow (Nardocci *et al.*, 1999). N-acetylgalactosaminidase deficiency (Schindler disease) may show clinical and histological findings similar to INAD and can be excluded by biochemical tests (Schindler *et al.*, 1989; Wolfe *et al.*, 1995). INAD and neurodegeneration with brain iron accumulation (NBIA) (also known as Hallervorden-Spatz disease) share pathological findings such as the axonal pathology resulting in spheroids formation and radiological features including the hypodensity in the pallida so typical of NBIA (Farina *et al.*, 1999). They differ, however, with respect to their course and clinical phenomenology. NBIA has a late-infantile or juvenile onset and patients may survive into their third decade; the main clinical features of NBIA are dystonia, parkinsonism and choreoathetosis while signs of extrapyramidal involvement are almost exceptional in INAD. Furthermore in INAD, but not in NBIA the dystrophic axons are also found in distal peripheral nerves, allowing for a pathologic discrimination *in vivo* (Malandrini *et al.*, 1995).

Etiology

Neuroaxonal dystrophy (NAD) characterized by axonal swellings and "spheroid bodies" throughout the central and peripheral nervous systems is the pathological hallmark of primary NAD (Jellinger, 1973, Seitelberger, 1986), although it is a feature shared by different clinical conditions. NAD includes INAD, late infantile, juvenile, and adult NAD, neuroaxonal leukodystrophy and NBIA. NAD is also seen in a number of degenerative disease such as Parkinson's disease, certain metabolic disorders such as Wilson's disease, Niemann-Pick disease and vitamin E deficiency. A defect in axonal transport has been suggested as a mechanism for spheroids formation (Wakai *et al.*, 1993; Kimura *et al.*, 1991; Itoh *et al.*, 1993). However, the presence of swollen axons in a distribution

consistent with dysfunction of the axon terminals had also suggested that deficits in synaptic transmission localized to the terminal axon might be involved (Walkley *et al.*, 1991). The pallidal hypointensity on MRI consistent with an accumulation of ferritin-bound iron occasionally observed in INAD patients raise the issue of the role that iron may play in the pathogenesis of INAD. A disturbance of iron protein functions, such as transport and delivery from and to cellular compartments could cause the pathological findings of this condition (Gelman, 1995).

Furthermore studies of oxidant stress in parkinsonian animal models suggest a linkage of iron overload to axonal dystrophy (Chiueh, 2001).

Clinical description

The onset of the disease usually occurs between the age of six months and 3 years. The initial symptom is a slowing of the rate of motor and mental development followed by a definite regression with loss of previously acquired milestones. Psychomotor regression is associated with increasing hypotonia with muscular weakness of such a degree as to suggest a diagnosis of myopathy or of spinal muscular atrophy. Muscle atrophy may be present, reflecting involvement of the lower motor neuron that may be responsible for the loss or diminution of deep tendon reflexes occurring in some patients. Pyramidal tract signs with extensor plantar responses are regularly present. Visual symptoms and signs, including strabismus, pendular nystagmus, incoordinate eye movements, optic atrophy and failing vision are generally early and prominent.

The progression of the motor and cognitive deterioration is usually rapid. Seizures are rare and usually a late and not prominent event (Aicardi *et al.*, 1979; Ramaekers *et al.*, 1987; Nardocci *et al.*, 1999; Santucci *et al.*, 2001). In some cases, ictal events may be non-epileptic in nature since paroxysms of opisthotonus or decerebrate rigidity are common and can mimic epileptic fits. Extrapyramidal signs are only rarely described (Gillmann *et al.*, 1973; Yagishita *et al.*, 1975; Simonati *et al.*, 1999; Kyllermann *et al.*, 2001). Terminally, bulbar signs with swallowing difficulties and dyspnea supervene. At this stage the patients are totally helpless, blind, tetraplegic and demented and death usually occurs before the age of 10 years. Diagnosis of INAD may be difficult since it may present with unusual features or because the predominant feature can be quite different from the classical form described above suggesting phenotypic variability. A protracted form characterized by the occurrence of neurological deterioration between 7 and 12 years, after a fairly stable

course resembling static encephalopathy, and by a hypotonic-areflexic tetraparesis without evidence of pyramidal dysfunction has been described (Nardocci *et al.*, 1999). Unusual features of INAD include microcephaly and rigid quadriplegia (Ramaekers *et al.*, 1987), association with osteopetrosis (Rees *et al.*, 1995) and patients in which behavioural symptoms characteristic of autism dominate the clinical picture (Weidenheim *et al.*, 2001).

Diagnostic methods
A definite diagnosis of INAD requires the demonstration of axonal spheroids by the histological study of brain, nerve and muscle, skin or conjunctival biopsy. Electron microscopy shows that spheroids contain granular and tubulo-granular material, degenerated cytoplasmic organelles and glycogen accumulation. The presence of spheroid bodies in both myelinated and unmyelinated axons is the most typical finding although not specific to INAD (Nardocci *et al.*, 1999) since it appears in other conditions including NBIA, infantile GM2 gangliosidosis. Niemann-Pick disease type C, Menkes disease, chronic vitamin E deficiency (Seitelberger, 1986; Ramaekers *et al.*, 1987). Therefore the diagnosis of INAD is based on the combination of neuropathologic and clinical findings (Aicardi *et al.*, 1979).
Neurophysiological studies may help clinical diagnosis. The presence of high amplitude, non reactive, fast rhythms at 16 to 22 Hz in the EEG both in sleep and in the waking state, although not specific, is highly suggestive for INAD in an appropriate clinical setting (Aicardi *et al.*, 1979; Nardocci *et al.*, 1999). Electromyographic (EMG) signs of denervation are an early characteristic of the disease and the most indicative finding for the diagnosis (Nardocci *et al.*, 1999). Nerve conduction velocities are usually normal (Aicardi *et al.*, 1979; Ramaekers *et al.*, 1987) but findings indicating a distal axonal-type sensorimotor peripheral neuropathy may be present in the advanced stages of the disease (Nardocci *et al.*, 1999). The electroretinogram (ERG) is unremarkable. Visual evoked potential studies (VEPs) are usually abnormal or extinct, but patients with normal VEPs have been reported (Aicardi *et al.*, 1979). Thus the association of normal ERG with extinct or reduced VEPs corroborates the diagnosis of INAD and the presence of a normal VEPs does not exclude the diagnosis in the appropriate clinical context.
Marked cerebellar atrophy, mainly involving the inferior part of the vermis, and signal hyperintensity of the cerebellar cortex on T2-weighted images are the most characteristic magnetic resonance imaging (MRI) findings observed in INAD patients (Barlow *et al.*, 1989; Ito *et al.*, 1989; Tanabe *et al.*, 1993; Farina *et al.*,

1999; Rodriguez *et al.*, 2001). These abnormalities may be detectable as early as 2 years of age and represent an important finding for the early suspicion of INAD because they have not been described in any other degenerative disease with the same age onset. The spectrum of MRI abnormalities observed in INAD patients is wide and includes cerebral cortical atrophy, hyperintensity of cerebral white matter, thinning of the optic chiasma, and signal hyperintensity in the dentate nuclei consistent with pathologic data (Jellinger, 1973; Seitelberger, 1986). Signal hypointensity of the globus pallidus in T2-weighted images probably related to iron deposition has been occasionally observed in INAD patients (Ito *et al.*, 1989; Farina *et al.*, 1999; Simonati *et al.*, 1999). These MRI findings are similar to those characteristics of NBIA (the "eye of the tiger sign") (Sethi *et al.*, 1988; Savoiardo *et al.*, 1993) indicating a radiological overlap between INAD and NBIA.

Epidemiology
The frequency of INAD is unknown.

Management
Due to the lack of knowledge about the etiology no specific treatment is available. A rehabilitation program including physiotherapy and orthopaedic management could be helpful and should be started early in the course of the disease. The main task of these therapies is to prevent the development of contractures and fixed deformities. Symptomatic pharmacological treatment of spasticity and seizures with myorelaxant and antiepileptic drugs may be of some benefit.

Unresolved questions
INAD and NBIA have several features in common. In particular, pathological examination shows axonal swelling and spheroid bodies in the central nervous system in both diseases. Since the first description of INAD there has been a discussion whether these syndromes are distinct entities or the extremes of a disease spectrum (Cowen *et al.*, 1963; Gillmann *et al.*, 1973). Mutations in the gene for pantothenate kinase 2 (PANK2) were identified as the genetic cause in the majority of NBIA patients (Zhou *et al.*, 2001), and cause pantothenate kinase-associated neurodegeneration, or PKAN, a subgroup of NBIA. Pantothenate kinase is a key regulatory enzyme in the synthesis of coenzyme A (CoA) from pantothenate indicating that PKAN is the result of a defect of pantothenate metabolism. Recently, a genetic study in seven INAD families revealed no mutations in PANK2 or in other genes of CoA biogenesis (Hortnagel *et al.*, 2004) strongly suggesting that INAD and PKAN are genetically heterogeneous disorders.

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