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Dementia means number of things – the overlap of neurodegeneration with brain iron accumulation (NBIA) and Alzheimer changes: an autopsy case

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Abstract

In humans overlap between various neurodegenerative disorders is a well known phenomenon. We reported a case of a 77-year-old woman with parkinsonism, dystonia, psychiatric symptoms and progressing dementia misdiagnosed at the age of 51 years as Parkinson's disease. Histopathological examination of the patient's brain performed 26 years after the disease onset revealed numerous axonal spheroids and iron deposits in structures of the nigro-pallido-striatal system that enabled to diagnose neurodegeneration with brain iron accumulation (NBIA) (former Hallervorden-Spatz syndrome), and changes characteristic for Alzheimer's disease (AD).

NBIA is a group of rare clinically and genetically heterogeneous diseases of the extrapyramidal system which common feature is abnormal iron storage in the basal ganglia. Disturbed iron metabolism is also one of the hypothetical pathomechanisms of AD. A coexistence of morphological changes characteristic for AD and NBIA in our patient suggests that similar molecular mechanisms may be involved in pathogenesis of various neurodegenerative processes, especially in disorders with iron dyshomeostasis. This case contributes also to the increasing evidence of NBIA heterogeneity.

Key words: Alzheimer's disease, amyloid plaques, NBIA, Hallervorden-Spatz syndrome, tangles.

Introduction

Neurodegeneration with brain iron accumulation (NBIA) (former Hallervorden-Spatz syndrome) comprises a clinically and genetically heterogeneous collection of disorders that share common key feature – iron storage in the basal ganglia. For decades, regardless of marked clinical heterogeneity, most patients with radiographic or pathologic evidence of iron accumulation in brain were given this diagnosis. In recent years introduction of genetic examination allowed to reclassificate this group of disorders due to various genetic mutations [6]:

1) autosomal recessive panthotenate kinase-associated neurodegeneration (PKAN) caused by mutations in gene encoding pantothenate kinase 2,
2) autosomal recessive aceruloplasminemia due to mutations in ceruloplasmin gene,

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3) cases with mutations in gene encoding phospholipase A2,
4) autosomal dominant neuroferritinopathy due to mutations in gene encoding the ferritin light chain (NBIA-2),
5) sporadic cases of the CNS degeneration with iron accumulation in which genetic background has not been identified (NBIA-1). These cases account for 75% of all cases of NBIA [15].

Similarity of NBIA clinical picture to symptoms and signs present in other neurodegenerative diseases, as well as a diverse morphological images and a presence of sporadic forms of the disorder makes that NBIA is rarely diagnosed. We reported of an atypical case of NBIA with very late onset at the age of 51 years, long duration (26 years) and uncommon morphological picture. Our case of NBIA illustrates the heterogeneity of the disorder and contributes to the increasing evidences of overlapping of pathomorphological changes in different neurodegenerative diseases.

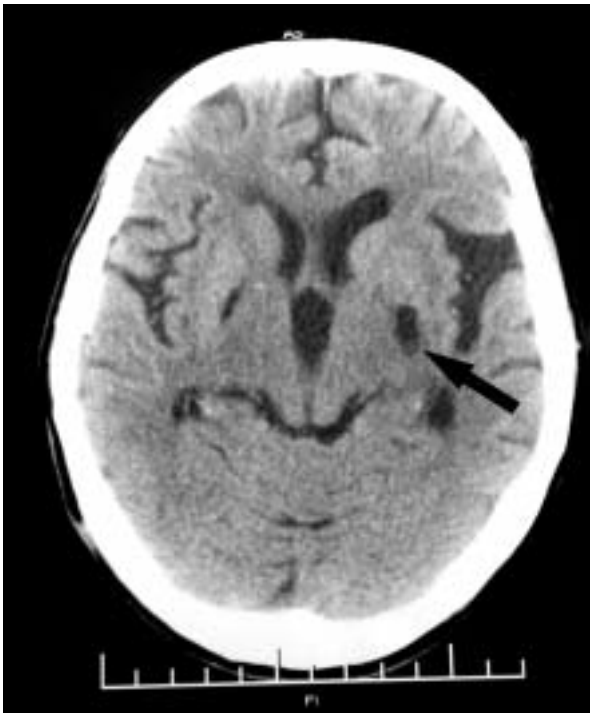

Fig. 1. Brain MRI scan shows generalized brain atrophy, bilateral lacunas in the basal ganglia with postoperative change in the right globus pallidus (arrow), and small vasogenic foci dispersed in the white matter.

Case report

A 77-year-old women with parkinsonism, psychiatric symptoms and progressing dementia was admitted to the hospital because of disturbances in consciousness and deterioration of the general state. The first symptoms of the disease appeared at the age of 51 years as rigidity and hypokinesia. Parkinson's disease (PD) was diagnosed and she received L-Dopa continued for the next eighteen years. The response for the treatment was described initially as rather poor then as non effective. At the age of 55 years hypersalivation and dystonia of the left hand was observed. Two years later motor dysfunction of the right upper limb and disturbances in memory, speaking and reading appeared. During next 10 years of relentlessly progressive course of the disease the patient developed dysarthria, posture problems, sudden falls, dysphagia, marked hypokinesia, insomnia, vision worsening, severe dyskinesias and depression. At the age of 69 years left pallidotomy was performed because of ineffectiveness of the L-Dopa treatment. During next years delusions, hallucinations, psychomotor agitation and periods of hypersomnia were observed. At the age of 76 years the patient was bed-ridden.

At the last admission to the hospital neurological examination revealed severe dementia, rigidity, mioclonic jerks and bilateral Babinski sign. Routine hematological, biochemical and cerebrospinal fluid examinations were within normal limits. In EEG pseudoperiodic generalized discharges were seen. Brain MRI scan revealed hypointensive changes in both globi pallidi, dispersed lacunar vasogenic foci and brain atrophy (Fig. 1). Four weeks after the admission to the hospital the patient died because of circulatory and respiratory insufficiency.

The patient's mother was diagnosed by general practitioner as PD and died 20 years after the disease onset at the age of 70 years.

On gross sectioning generalized brain atrophy and rust-brown pigmentation and cavities in both globi pallidi were seen (Fig. 2A). Pearl's stain detected iron accumulation in the substantia nigra and basal ganglia (Fig. 2D), mainly in the globi pallidi. Iron deposits were found around blood vessels (Fig. 2E), in glial cells, macrophages (Fig. 2F) and in scattered neurons. In cerebral hemispheres (Fig. 2B), cerebellum (Fig. 3C) and brain stem numerous axonal spheroids were seen. Spheroids were tau-ferritin-β amyloid negative but majority of them were immunoreactive to α-synuclein. In addition to iron deposition and spheroid

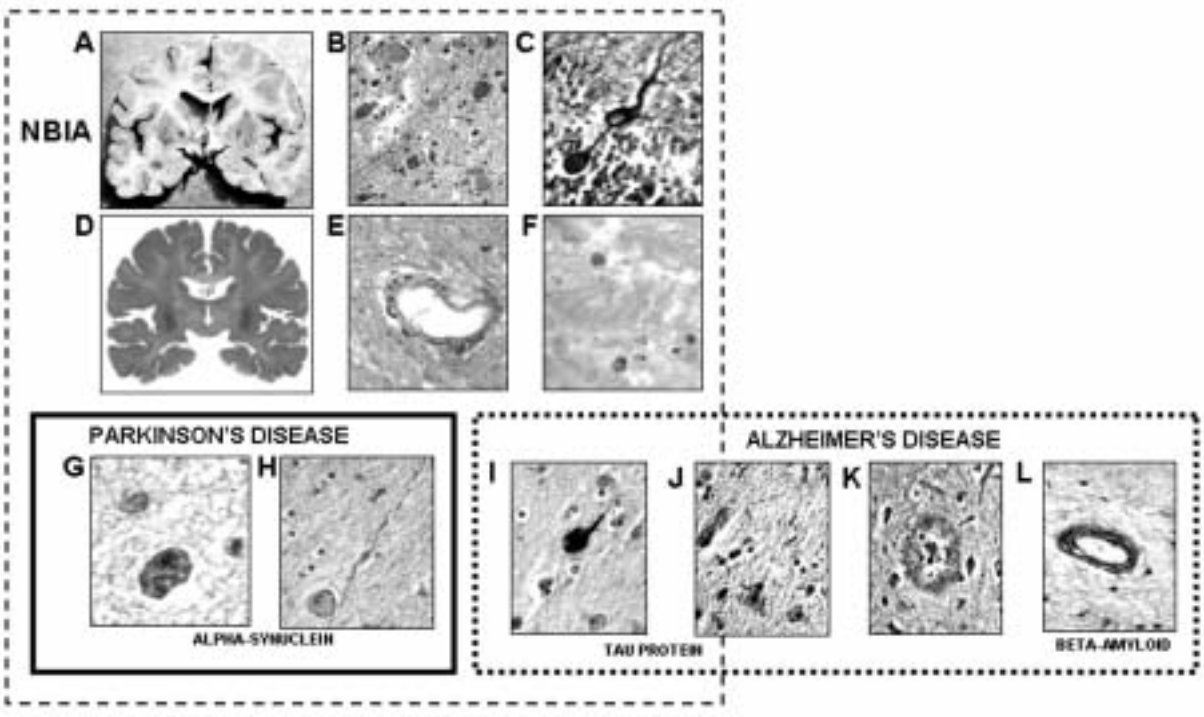

Fig. 2. A) Brain gross section demonstrates bilateral lacunas in the basal ganglia, **B**) numerous spheroids in the putamen; H&E, **C**) spheroid (torpede) in the cerebellar cortex; silver impregnation, **D**) iron accumulation in the basal ganglia; Perl's stain, **E**) perivascular iron accumulation in the globus pallidus; Perl's stain, **F**) intracellular iron accumulation in the putamen; Perl's stain, **G**) cytoplasmic neuronal inclusion immunoreactive to α-synuclein, **H**) α-synuclein-positive Lewy neurities in the midbrain, **I**) tau-positive neuron in the hippocampus, **J**) neuropil threads immunoreactive to tau protein in the subiculum, **K**) neuritic plaque in the temporal cortex, β-amyloid, **L**) depositions of β-amyloid in vessel wall of the temporal lobe.

formation, immunoreactive to α-synuclein Lewy body-like intraneuronal inclusions (Fig. 2G), dystrophic neurites (Fig. 2H) and extracellular deposits of α-synuclein were seen. They were observed in cerebral cortex, substantia nigra, nucleus locus ceruleus, and, less numerous, in cerebellum and other brain stem structures.

Substantia nigra and nucleus locus ceruleus revealed nearly total loss of neurons, extracellular deposits of neuromelanin and severe tissue spongiosis. Other neuropathologic findings included diffuse moderate demyelination of the white matter and neuronal loss in cerebral cortex with subsequent gliosis.

The immune reaction with antibodies to tau protein showed neurofibrillary tangles (Fig. 2I) localized mainly within transenthorinal cortex and neuropil threads (Fig. 2J) in the hippocampus and subiculum. According to Braak classification [3], localization of tangles was characteristic for stage I of AD. The immune reaction with antibodies to β-amyloid revealed numerous amyloid plaques in cerebral cortex (Fig. 2K) and vessel amyloidosis (Fig. 2L). Distribution of the amyloid and neuritic plaques was similar to the typical pattern for AD. The number of the plaques fulfilled the CERAD criteria for probable AD [9].

Although genetic examination was not performed, retrospective analysis of clinical symptoms and characteristic morphological changes enabled diagnose NBIA.

Discussion

We reported on a patient with an unusual late onset and long course of NBIA with mixed morphological changes in the brain fulfilling neuropathologic diagnostic criteria for NBIA and AD.

In humans overlap between various neurodegenerative disorders is a well known phenomenon.

Since PD pathology is involved in morphological picture of NBIA and has been described previously, the most interesting finding in the reported case is the coexistence of histopathological changes characteristic for AD and NBIA. Several papers on NBIA have reported a presence of tau-positive neurofibrillary tangles but, according to our knowledge, this is the first report wherein numerous amyloid plaques were also found.

Although coexistence of NBIA and AD may be accidental, there is also a possibility that a particular relationship exists between these two neurodegenerative diseases. Our case may be an unique manifestation of such relationship because usually NBIA patients die relatively early (in the young or middle age), so there is no enough time to develop pathology associated with aging process such as AD.

It is known that the maintenance of iron homeostasis is critical for the cell: iron deficiency impairs cell growth while iron overload can cause cellular damage. Characteristic feature for NBIA is abnormal iron deposition but this phenomenon has been reported not only in genetic disorders with mutations in the iron metabolic pathways, but also in many other neurodegenerative disorders including AD.

Dysregulation of brain iron homeostasis is one of the pathogenetical hypotheses in AD. In AD patients abnormalities in several proteins involved in cerebral iron transport have been described in several papers (references in: [12]). Investigations revealed defective ceruloplasmin, overexpression of lactoferritin, reduced level of iron-binding protein metallothionein III in astrocytes and significantly elevated level of other iron-binding protein, protein 97 (melanotransferrin) in cerebrospinal fluid. Moreover, a correlation between the increased concentration of melanotransferrin in the serum and the progression of AD was also observed.

In AD brains, increased concentration of iron was found in and around amyloid plaques [4,8] that suggests that iron accumulation may influence amyloid plaque formation [2]. β-amyloid is a high-affinity metalloprotein that easily aggregates in the presence of biometals such as iron [7]. It has been also demonstrated that iron can modulate amyloid precursor holo-protein expression [9]. Additional evidence of the involvement of iron metabolism in AD development is the finding that patients with transferrin subtype C2 and mutations in hemochromatosis gene HFE are more common in AD suffers than in general population [11,14], and the presence of the C2 variant plus the HFE mutation increased the risk of AD five-folded [13].

There are several possible relationships between development of AD and NBIA.

Firstly, the coexistence of NBIA and AD in the same patient may be connected with iron toxicity. Despite considerable investigations, it is still not clear whether excessive iron accumulation in NBIA is an initial event that causes neuronal death or is a consequence of the disease process. On the basis of current neuropathological evidences, it seems reasonable to suggest that iron accumulation is the first step in degenerative process in NBIA [15]. It is possible that iron accumulation in NBIA disrupts normal control mechanisms of amyloid and tau protein expression. Disturbances in iron metabolism leading to the metal accumulation cause generation of free radicals damaging cellular macromolecules. Abnormal proteins, in turn, may disturb critical cellular metabolic processes result in cell death. It is believed that free-radical pathway could be a common mechanism in many neurodegenerative diseases. So, iron dyshomeostasis could trigger independently both NBIA and AD in the same patient.

Secondly, it is possible that not iron but α-synuclein accumulation in NBIA may contribute to the development of AD. It was demonstrated that α-synuclein can induce fibrillation of tau protein and its co-incubation with tau synergistically induces aggregation of the proteins [5]. α-synuclein significantly stimulates also nitric oxide synthase (NOS) activity and, by oxidative stress, can trigger mitochondrial failure and cell death [1]. The same mechanisms may participate in development of Alzheimer's pathology in the course of NBIA and in this situation AD would be secondary to NBIA.

Thirdly, neurodegenerative disorders share not only similar metabolic processes but brain cells, particularly neurons, have a limited repertoire of response to injury. This narrow range of non-specific reactivity makes that certain neurons can display fibrillary aggregats typical for two or more different diseases.

In summary, although it has been still unknown whether NBIA can give rise to AD or both disorders develop independently, their coexistence may not only contribute to the increasing evidences of the overlap in various neurodegenerative diseases but in the future may confound also their classification.

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