CLINICOPATHOLOGICAL VARIABILITY IN NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

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KLINIKOPATOLÓGIAI VARIABILITÁS VASLERAKÓDÁSSAL TÁRSULÓ NEURODEGENERÁCIÓBAN
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Neurodegeneration with brain iron accumulation (NBIA) is a rare, progressive neurodegenerative disorder with extrapyramidal and cognitive clinical symptoms characterized by iron accumulation predominantly in the globus pallidus, as well as extensive axonal spheroids in various regions of the brain. Recent studies indicate multiple genetic causes, however the illness can occur without obvious genetic background. The most frequent genetic form is the pantothene kinase associated neurodegeneration (PKAN) with mutation in the pantothenate kinase 2 *(PANK2)* gene. Further forms include phosphoslipase A2 *(PLA2G6)* gene mutation, neuroferritinopathy, and aceruloplasminaemia. To demonstrate the phenotypic variability associated with NBIA we present two patients. In the first patient iron deposition in the globus pallidus and axonal spheroids throughout the whole brain confirmed the neuropathological diagnosis of NBIA. Based on the long duration (27 years), the relatively late onset (at age of 13) of the disease, and the symmetrical hypointensity in the globus pallidus, without the eye-of-the-tiger sign in cranial MRI, this case most likely represented an idiopathic form of NBIA but atypical PKAN may be also considered. In our second patient, who is still alive after duration of 9 years, MRI revealed the typical eye-of-the-tiger phenomenon that supported the clinical diagnosis of NBIA and was highly suggestive of PKAN. Since NBIA shows similarities with other neurodegenerative disorders, genetic examination may be essential in the diagnosis of this disease, however, cranial MRI together with the clinical picture may be highly indicative of NBIA.

Keywords: *neurodegeneration with brain iron accumulation, eye-of-the tiger sign, panthothenate kinase-associated neurodegeneration (PKAN)*

A vaslerakódással járó neurodegeneráció (NBIA) ritka, progresszív neurodegeneratív betegség, amelyet extrapyramidalis és kognitív zavarok jellemeznek. A neuropatológiai diagnózis alapja a globus pallidusban látható vaslerakódás, valamint a szinte minden agyi régióban előforduló neuroaxonalis spheroidok. A betegség oka legtöbbször valamilyen genetikai defektusra vezethető vissza, de előfordulhat nyilvánvaló genetikai eltérés nélkül is. A leggyakoribb genetikai eredetű formában (panthothenate kinase-associated neurodegeneration, PKAN) a pantoténkináz enzimet kódoló génben *(PANK2)* mutatható ki mutáció. További genetikai formák a foszfolipáz enzim gén *(PLA2G6)* eltéréshez kapcsolt, a neuro-ferritinopathia, illetve az aceruloplasminaemia. Két esetet mutatunk be. Az elsőben a neuropatológiai vizsgálat során a globus pallidusban észlelt vaslerakódás, valamint a szinte minden agyi régióra kiterjedő neuroaxonalis spheroidok jelenléte alátámasztotta az NBIA diagnózisát. MR-vizsgálat során nem láttunk „tigrisszem-elváltozást", de szimmetrikus jelintenzitás-csökkenés volt mindkét oldali globus pallidus területén. Figyelembe véve a betegség hosszú lefolyását (27 év), viszonylagos késői kezdetetét (13 év), illetve a neuropatológiai, valamint képalkotó viszgálatok eredményeit, a legvalószínűbb diagnózis a betegség idiopathiás vagy atípusos PKAN formája. A másik esetben kilenc éve kezdődött a kórkép. Az MR-vizsgálat kimutatta a típusos „tigrisszem-elváltozást", amely jellemző a PKAN-formára. Mivel a vaslerakódással járó neurodegeneráció hasonlíthat más neurodegeneratív kórképre, a genetikai vizsgálat fontos a betegség pontos diagnosztikájában, de MR-vizsgálat megfelelő klinikai kép esetén valószínűsítheti a kórismét.

Kulcsszavak: *vaslerakódással társuló neurodegeneráció, „tigrisszem-elváltozás", pantoténkináz enzimdefektussal társuló neurodegeneráció (PKAN)*

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Neurodegeneration with brain iron accumulation (NBIA) is a group of rare, progressive, neurodegenerative disorders with extrapyramidal and cognitive clinical symptoms. It is characterized by iron accumulation predominantly in the globus pallidus and the pars reticulata of the substantia nigra, as well as extensive axonal spheroids in various regions of the brain. Recent studies indicate various genetic causes, however the illness can occur without obvious genetic background suggesting further multifactorial genetic and environmental causes.

The name NBIA encompasses the spectrum of disorders previously called Hallervorden–Spatz disease or syndrome, which was first described by Julius Hallervorden and Hugo Spatz. They reported a syndrome in 1922 with deposition of iron in the globus pallidus and pars reticulata of the substantia nigra. The primary symptoms were gait difficulties, rigidity of leg, and feet deformity. Afterwards progressive dementia and dysarthria developed. The patients died between the ages of 16 and 27 years[1]. The term Hallervorden–Spatz disease was changed because of their unethical activity during the World War II[2, 3].

In the present paper we review current knowledge on NBIA and we aim to demonstrate the variability of these disorders by reporting clinical data on two and neuropathologic in one patient.

Classification and genetic background

Up till now there are approximately 140 published cases. The disorder appears in every ethnic group and also occurs in both sexes equally[4]. Consanguinity is a risk factor for NBIA. Familial involvement, usually an autosomal recessive pattern, may be demonstrated in about 50% of the patients[5]. Gregory et al. suggested two main groups: an early-onset, rapidly progressive, and a late-onset, slowly progressive form (**Table 1**)[5]. The most frequent genetic form is the pantothene kinase associated neurodegeneration (PKAN) accounting for about 50% of all NBIA cases[5], with mutation in the pantothenate kinase 2 (*PANK2*) gene. Further genetic forms include neuroferritinopathy caused by the mutation of ferritin light polypeptide (*FTL*) gene[6]; aceruloplasminaemia caused by the mutation of ceruloplasmin (*CP*)[7]; phosphoslipase A2 (*PLA2G6*) gene mutation[8] that is associated with infantile neuroaxonal dystrophy (INAD) and atypical neuroaxonal dystrophy (NAD)[9].

Table 1. *Classification of neurodegeneration with brain iron accumulation (NBIA)*

Early onset, rapid progressive forms	Late onset, slowly progressive forms
Classic PKAN (PANK2)	Atypical PKAN (PANK2)
INAD, Seitelberger's disease (PLA2G6)	Neuroferritinopathy (FTL)
Atypical NAD (PLA2G6)	Aceruloplasminaemia (CP)
Idiopathic NBIA	Idiopathic NBIA

PKAN: pantothenate kinase associated neurodegeneration; *PANK2*: pantothenate kinase 2 gene; INAD: infantile neuroaxonal dystrophy; NAD: neuroaxonal dystrophy; *PLA2G6*: phospholipase A2 group VI gene; *FTL*: ferritine light polypeptid gene; *CP*: ceruloplasmin gene.

Pathogenesis

Mutation in *PANK2* and *PLA2G6* genes highlight the importance of phospholipid and fatty acid metabolism. Phospholipase A2 takes an important part of phospholipid remodeling, which is necessary for maintenance and repair of cellular membranes[10]. In patients with the mutation of *PANK2* gene increased level of cystein can be observed, which can trigger Fe-catalyzed oxidative reactions[11] providing a pathomechanism of iron accumulation in affected cells.

In a study, dated before the introduction of genetic analysis, cystein-deoxygenase deficiency was detected in particularly in the globus pallidus and the pars reticulata of the substantia nigra in two human brains with NBIA[12]. This observation suggests that high level of cystein can cause direct toxicity by altering normal reaction with iron and generating toxic free radicals. On the other hand, impaired cystein metabolism may reduce neuromelanogenesis. These two mechanisms may play an important role in the development of NBIA syndrome. Synergic mechanism of iron and cystein in lipid peroxidation was verified by an *in vitro* study in liver microsomal system. Although iron and cystein have potential for lipid peroxidation separately, when they were added together, lipid peroxidation was greater than the sum of the amounts formed[13].

The fact that serum levels of iron, ferritin, transferrin and coeruloplasmin are mainly in the normal range suggests that iron metabolism affects selectively the brain, which could lead to secondary damage of the globus pallidus and pars reticulata of substantia nigra[14], since these regions contain the highest amount of iron in normal brain.

Diagnostic procedure

The diagnosis of NBIA and its classification can be challenging. Symptoms of NBIA may develop for several years. The most common features are progressive mental impairment, gait instability, rigidity, dysarthria, and corticospinal tract involvement. Parkinsonism may be detected in the late-onset form, whereas dystonia occurs more frequently in early-onset patients[4]. Alternating episodes with rapid progression, lasting one or two months, and longer stable periods are described[15]. Although the disease can develop at any age, the onset is often in early childhood, or at least under 30 years of age. Peripheral iron metabolism including serum iron, ferritin, and transferrin levels, is usually within the normal range, but patients may have palpable liver and/or spleen. Ferritin levels are lower in patients with mutation in the neuroferritin gene (*FTL*)[6]. EEG often shows normal activity, but in long-lasting cases, there are abnormalities such as generalized slowing, and abnormal theta waves. In NBIA T2 weighted MRI shows symmetric hypointensity in the globus pallidus. Importantly, symmetrical hypointensity in the globus pallidus with a central region of hyperintensity, also called as the "eye-of-the-tiger" sign is strongly indicative of PKAN[5]. To classify NBIA, genetic analysis of *PANK2, PLA2G6, FTL* and *CP* are advised.

In summary, after suspicion of NBIA (abnormal gait, falling, dystonia, dysarthria) cranial MRI should be performed: 1. If the eye-of-the-tiger sign is observed analysis of *PANK2* gene is suggested. 2. If hypointensity in the globus pallidus and/or substantia nigra is seen, it is most likely due to idiopathic NBIA, but to rule out PKAN consideration of *PANK2* gene analysis is still indicated. 3. If hypointensity in globus pallidus is associated with cerebellar atrophy molecular testing for *PLA2G6* mutation should be performed. If the genetic analysis for *PLA2G6* is negative further genes (e.g. *FTL, CP*) should be analysed before idiopathic NBIA is diagnosed.

Treatment possibilities

Although there is a lack of causative treatment, there are possibilities to decrease additional symptoms or to slow the progression. Earlier, iron binding drugs were tried[15]. Recently it was reported that a chelating agent called deferiprone reduced involuntary movements and blepharospasm[16]. Further palliative treatments include baclofen therapy, application of botulinum toxin, or even deep brain stimulation[5]. Antioxidants such as vitamin E, or vitamin B5 were also tried[5, 16, 17]. Patients with PKAN do not benefit from L-dopa therapy, but patients with non-PKAN NBIA and parkinsonism may respond[5].

Neuropathology

Macroscopically the most frequent lesions are the rust-brown pigmentation of the globus pallidus and pars reticularis of the substantia nigra. In the infantile variant of the NBIA cerebellar atrophy may be noted. Histological examination with specific iron stainings such as Prussian-blue confirms iron deposition in the globus pallidus, putamen, and the pars reticulata of the substantia nigra. Several axonal swellings called spheroids are seen in various regions. In INAD, spheroids can be detected also in the spinal nerve roots. Genetic forms may show similar neuropathologic appearance, but neuroferritinopathy and aceruloplasminaemia differs. In neuroferritinopathy, iron deposits occur throughout the forebrain, and most of them are also immunopositive for ferritin. Iron and ferritin are usually located extracellularly but also observed in microglia, oligodendroglia, as well as in neurons[6]. In aceruloplasminaemia, iron deposition can be detected in astrocytes. The most characteristic neuropathological features are deformity of astrocytes and globular structures immunoreactive for anti-ubiquitin and anti-4-hydroxynonenal (indicator of lipid peroxidation)[18].

Some studies on NBIA demonstrated pathological deposition of alpha-synuclein and phospho-tau[19–24]. It must be noted that the latter studies were performed mainly in NBIA cases that were not characterized genetically, thus association of alpha-synuclein and phospho-tau pathology with PKAN needs confirmation.

Extraneuronal changes include ophtalmopathy with total loss of outer, and nearly total loss of inner segment of photoreceptor cells, impaired motility of sperms, and bone marrow macrophages with ceroid lipofuscin[17].

Material and methods

CLINICAL EVALUATION

Two patients were examined. Both underwent neurological and psychiatric evaluations. Neuroimaging examination included CT and MRI scans of the brain in both.

Table 2. *Clinical and radiologic data on the two patients*

Case	Patient-1	Patient-2
Gender	male	female
Age at onset	12 years	2 years
Duration of illness	27 years	>10 years
Age at death	39 years	still alive/12 years old
Presenting symptoms		
Gait disturbance	+	+
Fatigue	+	–
Symptoms during disease course		
Invert rotation of feet	+	+
Mental decline/retardation	+	+
Nystagmus	+	+
Supranuclear gaze palsy	+	–
Spasticity	+	+
Pyramidal signs	+	+
Distal hypesthesia	+	–
Distal paresis and atrophy	+	–
Seizures	+	+
Dysarthria	+	–
Dysphagia	+	+
Hypomimia	+	–
Dystonia	–	+
Ballismus	–	+
Incontinence	+	+
MRI	hypointensity in GP	eye-of-the-tiger sign

GP: globus pallidus.

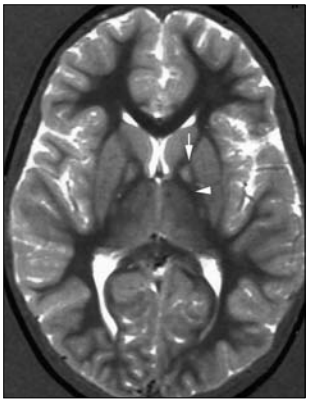

Figure 1. *T2-weighted brain magnetic resonance imaging showing hypointensity (white arrowhead) in the globus pallidus with a central region of hyperintensity (white arrow) compatible with the eye-of-the tiger sign*

NEUROPATHOLOGY

Neuropathological examination was performed in one patient (patient-1). Formalin-fixed, paraffin-embedded blocks were obtained from the following regions: frontal, cingulate, temporal, parietal, occipital cortices and subcortical white matter, basal ganglia, thalamus, hippocampus, amygdala, cerebellum, and brainstem at different levels. Sections were stained using hematoxylin and eosin, luxol fast blue, Prussian-blue, modified Bielschowsky and Gallyas methods. Immunohistochemistry (IHC) was carried out using the following monoclonal antibodies (mAb): anti-tau AT8 (1:200, Pierce Biotechnology, Rockford, IL, USA, pS202/pT205), anti-β-amyloid (1:100, Novocastra Lab. Ltd. Newcastle, UK), anti-HLA-DR (1:100, Dako), and anti-α-synuclein (1:10,000, clone 4D6, Signet, Dedham, MA, USA). In addition, polyclonal anti-glial fibrillary acidic protein (GFAP, 1:3,000, Dako) was used.

Results

CLINICAL OBSERVATIONS

Clinical data of two patients are summarized in **Table 2**.

Common features included early gait disturbance and mental decline or retardation. Nystagmus, dysphagia or dysarthria, seizures, deformated foot, and pyramidal signs were observed in both. In one patient senso-motor neuropathy was also detected, while in the young girl dystonia was prominent. Muscle biopsy of the right deltoid muscle revealed neurogenic changes and there were no ragged-red fibers. Both patients progressed to a bed-ridden state with incontinence. Disease duration was 27 years in the young man (patient-1) who died due to pneumonia at the age of 39 years, while the girl (patient-2) is alive after 9 years duration. MRI showed the typical tiger-eye phenomenon only in patient-2 (**Figure 1.**), but hypointensity in the globus pallidus in T2 was noted in patient-1. Kaiser–Fleischer ring was absent in both and laboratory variables including iron, copper, coeruloplasmin and lactate levels were in the normal range. Therapy included palliative therapy in both, in-cluding pyridostigmin for motility dysfuncion of oesophagus, carbamazepine for seizures and baclofen against spasticity. Genetic examination was performed in patient-1 to exclude Friedreich ataxia, which excluded a mutation. In the first-degree relatives there was a lack of any kind of neuropsychiatric disease.

Table 3. *Summary of histopathological findings*

	Alpha-synuclein IR		Tau IR			APP IR spheroids		GFAP IR	HLA–DR IR	
	NCI	Spheroids	Neurites	Pretangle	NFT	Small	Large	gliosis	Macrophage	Microglia
Frontal cortex	+	–	+	+	–	–	–	++	+	++
Cingular cortex	+	+	–	+	+	–	–	++	+	++
Temporal cortex	+	++	+	+	–	+	–	++	++	++
Parietal cortex	–	++	+	+	+	–	–	+	+	++
Occipital cortex	–	+	–	–	–	–	–	+	++	+
Motor cortex	–	–	–	–	–	++	–	–	–	–
Nucleus basalis Meynert	–	–	+	+	+	–	–	–	+	+
Thalamus med.	–	–	+	–	–	–	–	+++	++	+++
Cerebellar cortex	–	–	–	–	–	–	–	–	+	++
Nucleus dentatus	–	+	–	–	–	–	–	–	–	++
Nucleus caudatus	–	+	+	+	–	+	+	+++	+	+++
Globus pallidus	–	+++	+	–	–	+++	++	–	+++	+
Putamen	–	+++	++	+	–	+++	++	+++	+	+++
Amygdala	–	++	++	++	++	++	+	++	++	++
CA1	–	–	+	+	++	+	–	++	+	+
CA 2/3	–	–	++	+++	+	+	–	+++	+	+
Hilus	–	–	++	+	+	+	–	+++	+	+
Gyrus dentatus	–	–	+	–	–	+	–	+	–	–
Subiculum	–	–	+	++	–	+	–	+	+	+
Entorhinal cortex	+	+	+	–	++	++	–	+	+	++
Substantia nigra	–	+	+	–	+	+	+	+	++	+
Tectum	–	+	–	–	–	++	+	+	++	++
Dorsal raphe	–	–	–	–	+	–	+	+	+	++
Locus coeruleus	–	–	+	–	+	+	–	–	+	++
Pons basis	–	+	–	–	–	+	++	–	++	++
Dorsal vagus nucleus	–	–	–	+	–	+	+	–	+	+++
Inferior olive	–	–	–	–	–	+	–	–	–	+

NCI: neuronal cytoplasmic inclusion; NFT: neurofibrillary tangles; APP: amyloid precursor protein; GFAP: glial fibrillary acidic protein; HLA–DR: human leukocyte antigen–DR; CA: Cornu ammonis – Ammon's horn; –: no positivity; +: few/mild; ++: moderate; +++: abundant/severe.

NEUROPATHOLOGY

Major histopathological findings are summarized in **Table 3**. Briefly, severe neuronal loss, astro- and microgliosis were observed mainly in the globus pallidus, dentate nucleus, entorhinal cortex, caudate nucleus, and cerebellar cortex, including loss of Purkinje cells. Neurons in the brainstem tegmentum and inferior olives were relatively well preserved. Macrophages were detected mainly in the globus pallidus, amygdala, temporal and occipital cortex, substantia nigra, and in the tectum. Abundant pigment deposition was seen in the globus pallidus (**Figure 2. A**).

Axonal spheroids were detected in nearly all examined regions (**Figure 2. B**). According to immunostaining for APP, spheroids were divided into two groups by size (**Figure 2. C**). Small spheroids were detectable in many examined brain regions, while large spheroids were seen mainly in the globus pallidus, substantia nigra, and other brainstem structures (**Table 3.**).

Alpha-synuclein immunoreactive neuronal cytoplasmic inclusions (NCI) were very rare and observed only in the frontal, temporal, cingular (**Figure 2. D**), and entorhinal cortex. Typical Lewy-bodies were not detected. Many spheroids were immunoreactive for alpha-synuclein.

Mild to moderate numbers of phospho-tau-immunoreactive neuropil threads and dystrophic neurites (**Figure 2. E**) were seen in the basal ganglia, hippocampal formation, nucleus caudatus, and the frontal, temporal, and parietal cortex (**Table 3.**). Pretangles were seen in several regions of brain including basal ganglia, amygdala, frontal, cingular, temporal and parietal cortex, dorsal vagal nucleus, Ammon's horn, and subiculum. Abundant number of pretangles existed in the CA2 and CA3 pyramidal layers of Ammon's horn (**Figure 2. F**). Classical neurofibrillary tangles were detected in

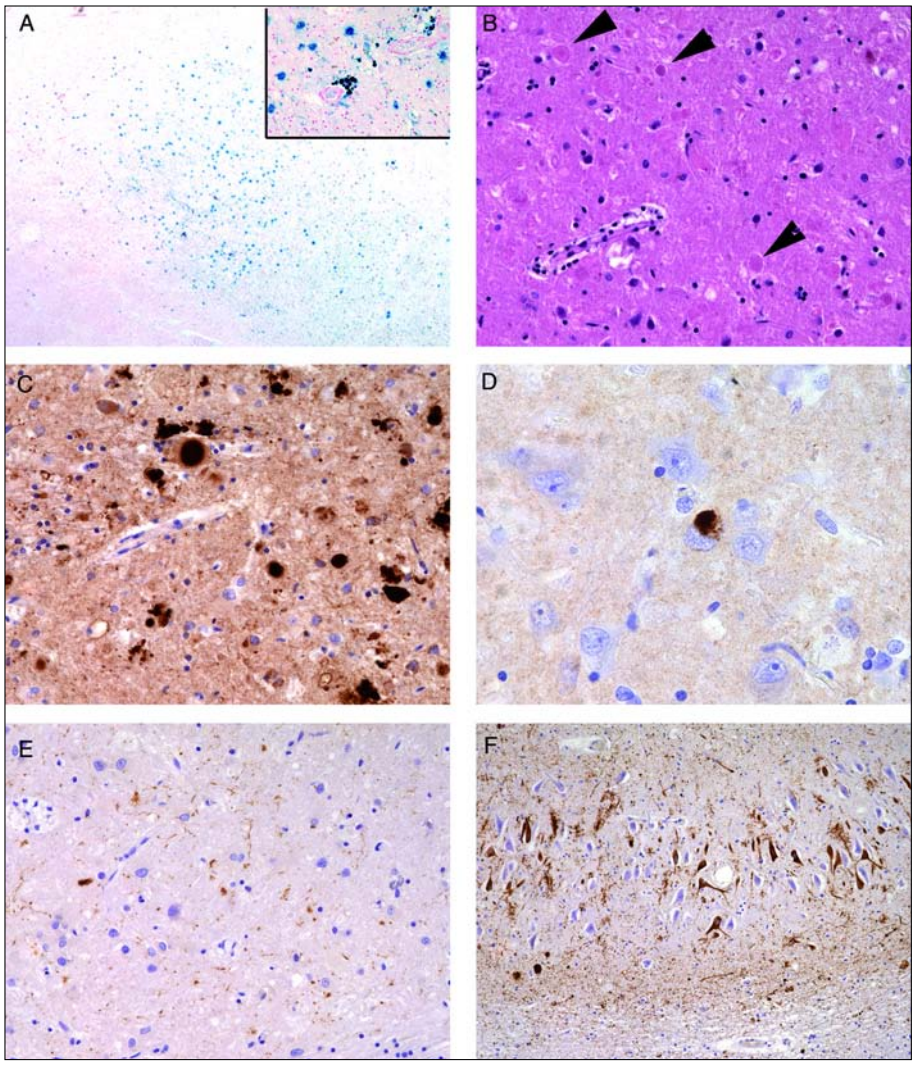

Figure 2. A *Prussian blue staining of the globus pallidus (×5) indicating iron deposition (blue; enlarged in right upper inset, ×20).* **B** *Numerous axonal spheroids (indicated also by arrowheads) in the globus pallidus (hematoxylin and eosin staining, ×20).* **C** *Immunostaining for amyloid precursor protein (APP) labels numerous large and small axonal spheroids in the globus pallidus (×20).* **D** *Neuronal cytoplasmic inclusion in the cingular cortex immunolabelled with anti-alpha-synuclein (×40).* **E** *Phospho-tau immunoreactive threads and neurites in the putamen (×20).* **F** *Prominent tau-pathology in the hippocampus: threads and diffuse cytoplasmic immunoreactivity in neurons*

the pyramidal layer of hippocampus, in the entorhinal cortex, substantia nigra, dorsal raphe nucleus, and locus coeruleus. Glial tau immunoreactivity was not observed.

Discussion

NBIA is a rare and progressive neurodegenerative disease. Although most cases have been described by neuropathological studies, clinical and neuroradiological recognition is crucial and may help in the evaluation of the genetic background. One most important feature is the "eye-of-the-tiger" phenomenon in MRI, which is often related to the PKAN form of NBIA.

To demonstrate the phenotypic variability associated with NBIA we presented two patients. In one case (patient 1) both clinical and neuropathological examinations were performed. Although the onset and duration of the disease were unusual, iron depositions in the globus pallidus and axonal spheroids throughout the whole brain confirmed the neuropathological diagnosis of NBIA. Based on the long duration (27 years), the relatively late onset (at age of 13) of the disease, and the symmetrical hypointensity in the globus pallidus in cranial MRI, this case most likely represented an idiopathic form of NBIA. Although genetic analysis was not available, atypical PKAN may be also considered. Speech difficulty is more frequent and motor disturbances are generally less severe in atypical PKAN cases[5], as observed in our case. Detection of hypesthesia and an electrophysiological demonstration of impaired nerve conduction velocity were only described in INAD cases. However, other clinical features and particularly the age of the patient were not compatible with INAD.

In this case, in addition to routine stainings, we performed immunostainings in order to better understand of the distribution of protein deposition (alpha-synuclein, phospho-tau), and glial pathology in NBIA. Most of the cases in the literature shows only tau-[19], or only alpha-synucleinopathy[20, 23]. In addition there are few reports about both proteinopathy[21, 25]. In our case both tau- and alpha-synucleinopathy was observed. Protein deposits were detected in basal ganglia, substantia nigra, and hippocampal formation similar to other studies[25]. The most severe gliosis was observed in the basal ganglia and substantia nigra, which showed activated microglia and macrophages as well.

Our second patient (patient 2) is still alive after duration of 9 years. Genetic evaluation was not available. MRI showed the typical tiger-eye phe-

nomenon that supported the clinical diagnosis of NBIA and is highly suggestive of PKAN[5]. Without genetic diagnosis, lack of cerebellar atrophy does not support *PLA2G6* mutation-associated NBIA (INAD). Symptoms of both PKAN and INAD are characterized by early gait disturbances, and dysarthria, dysphagia, and spasticity are common features. Both *PLA2G6* and *PANK2* mutation play an important role of lipid peroxidation[11, 26] resulting in a more transparent plasma membrane for iron entry suggesting a common pathogenetic pathway. Signs of cerebellar atrophy in MR images and indentification of axonal spheroids in peripheral nerve may be helpful to distinguish INAD (*PLA2G6* mutation)[9].

In conclusion, discovery of genetic alterations, in particular of *PANK2* and *PLA2G6* mutations in patients affected with NBIA provide a tool for molecular diagnosis after suspicion of the diagnosis using cranial MRI. It also indicates common pathogenetic pathways including lipid peroxidation, secondary cystein and iron toxicity, and oxidative stress leading to common or overlapping neuropathological alterations. Further morphological studies are needed to elucidate the exact pathogenesis and to evaluate variable forms of NBIA, which may lead to novel therapeutic options. Since NBIA shows similarities with other neurodegenerative disorders, genetic examination may be essential in the diagnosis of this disease.

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