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Review article

Update on neurodegeneration with brain iron accumulation

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ARTICLE INFO

Article history:
Received 27 March 2014
Accepted 6 May 2014
Available online 17 May 2014

Keywords:
NBIA
PKAN
PLA26G
Eye of the tiger sign

ABSTRACT

Neurodegeneration with brain iron accumulation (NBIA) defines a heterogeneous group of progressive neurodegenerative disorders characterized by excessive iron accumulation in the brain, particularly affecting the basal ganglia. In the recent years considerable development in the field of neurodegenerative disorders has been observed. Novel genetic methods such as autozygosity mapping have recently identified several genetic causes of NBIA. Our knowledge about clinical spectrum has broadened and we are now more aware of an overlap between the different NBIA disorders as well as with other diseases. Neuropathologic point of view has also been changed. It has been postulated that pantothenate kinase-associated neurodegeneration (PKAN) is not synucleinopathy. However, exact pathologic mechanism of NBIA remains unknown. The situation implicates a development of new therapies, which still are symptomatic and often unsatisfactory. In the present review, some of the main clinical presentations, investigational findings and therapeutic results of the different NBIA disorders will be presented.

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Neurodegeneration with brain iron accumulation (NBIA) defines a heterogeneous group of progressive neurodegenerative disorders characterized by excessive iron accumulation in the brain, particularly affecting the basal ganglia [1]. The pantothenate kinase-associated neurodegeneration (PKAN, previously named as Hallervorden–Spatz disease) and PLA2G6-associated neurodegeneration (PLAN) are the two main syndromes. Furthermore, novel genetic methods such as autozygosity mapping have recently identified several other genetic causes of NBIA [2] (Table 1). NBIA syndromes pose a challenge to the clinicians due to their complex phenomenology as well as their requirement for a comprehensive treatment. This review was prompted by the considerable development in this field. Some of the main clinical presentations, investigational findings and therapeutic results of the different NBIA disorders will be presented in the following review.

1. Pantothenate kinase-associated neurodegeneration (PKAN) – NBIA Type 1

The major form of NBIA is pantothenate kinase-associated neurodegeneration (PKAN), previously known as Hallervorden–Spatz disease (HSD). HSD was first described by the

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http://dx.doi.org/10.1016/j.pjnns.2014.05.001

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Table 1 – Neurodegeneration with brain iron accumulation (NBIA) [2,79,80].

NBIA	Mutated gene	Chromosomal localization
Pantothenate kinase-associated neurodegeneration (PKAN)/NBIA1[b]	*PANK2*[a]	20p13
PLA2G6-associated neurodegeneration (PLAN)/NBIA2, PARK14	*PLA2G6*[c]	22q12
Aceruloplasminemia (Acp)	*CP*[d]	3q23
Neuroferritinopathy	*FTL*[e]	19q13
FA2H – Associated Neurdegeneration (FAHN)/SPG35[g]	*FA2H*[f]	16q23
Kufor-Rakeb Disease NBIA3/(PARK9)	*ATP13A2*	1p36
Mitochondrial membrane protein associated neurodegeneration (MPAN)	*C19orf12*	19q12
Static encephalopathy of childhood with neurodegeneration in adulthood (SENDA syndrome)	nk[h]	nk

[a] Pantothenate kinase 2.
[b] Neurodegeneration with brain iron accumulation.
[c] Phospholipase A2.
[d] Ceruloplasmin.
[e] Ferritin light chain.
[f] Fatty acid 2-hydroxylase.
[g] Spastic paraplegia.
[h] Not known.

German neuropathologists Julius Hallervorden and Hugo Spatz in 1922 [3]. It should be stressed that because of their criminal activities during World War II (participating in Nazi T4 program of euthanasia), HSD is now referred to as PKAN [4]. PKAN is an autosomal recessive disorder caused by mutations in *PANK2* gene [5] which is located on chromosome 20p [6]. The exact pathologic mechanism of PKAN remains unknown. *PANK2* encodes pantothenate kinase 2, which is a regulatory enzyme in the coenzyme A (CoA) biosynthesis and catalyzing the phosphorylation of pantothenate (vitamin B5), *N*-pantothenoyl-cysteine, and pantetheine. CoA plays an essential role in fatty acid synthesis and energy metabolism. It has been postulated that decreased level of panthotenate kinase 2 leads to the accumulation of cysteine-containing neurotoxic substrates, mostly in the regions with higher energy demand, such as the basal ganglia [1,5]. Excess amounts of cysteine, chelate iron and form a complex which leads to tissue damage by promoting oxidative stress [7]. PKAN accounts for approximately 50% of cases of NBIA [1]. According to the time of onset, PKAN has been classified as early onset, rapidly progressive classic disease and late onset, slowly progressive atypical variant.

2. Classic PKAN

In the classic form, onset occurs between 3 and 4 years of age. Extrapyramidal dysfunction with prominent dystonia as well as gait and postural difficulties are usually the most prominent syndromes [1] with early involvement of oromandibular region by dystonic symptoms and signs [8]. Moreover, parkinsonism, chorea, acanthocytosis, cognitive decline and dementia might be present. Other common features include involvement of the corticospinal tract with spasticity, hyperreflexia and pathologic signs, dysarthria and clinical or electroretinographic evidence of pigmentary retinopathy [1,9]. Egan et al. demonstrated that Adie's-like pupils, vertical saccades, and saccadic pursuits are common, what suggests that midbrain degeneration frequently occurs in PKAN. Additionally, square wave jerks, poor convergence, abnormal vertical optokinetic response and inability to suppress the vestibule-ocular reflex may be present. There was no evidence of optic atrophy [10]. Supranuclear gaze palsy has also been reported in PKAN patient [11]. The loss of ambulation occurs within 10–15 years after the onset of the disease [1].

3. Atypical PKAN

The onset takes place between the second and the third decades [1]. Atypical disease is clinically heterogeneous [12]. Speech difficulties (palilalia, dysarthria) and psychiatric problems are frequent the initial syndromes. Extrapyramidal features are generally less severe and more slowly progressive than patients with classic form [1,7]. It has been reported that patients with adult onset PKAN often present parkinsonism as the first sign whereas early onset individuals seem to have dystonia as a presenting feature [7]. Psychiatric syndromes include personality changes with impulsivity and violent outbursts, depression, obsessive-compulsive signs and emotional lability [13,14]. The presence of psychotic symptoms has also been described in the literature [15–18]; cognitive decline and dementia may also develop [1]. Moreover, pyramidal tract involvement [12], freezing during ambulation and pure akinesia can be observed [19,20]. Sleep analysis revealed altered sleep architecture with reduced total time of sleep and the lack of slow wave sleep. No significant apnea/hypopnea and REM sleep abnormalities – in particular REM sleep behavior disorders were detected [21]. Diagnostic criteria for PKAN were first proposed by Dooling et al. and based on clinical features [22]. Swaiman revised these after brain MRI became a valuable diagnostic tool [23,24]. Gregory et al. suggest that after identification of *PANK2* gene and the development of the molecular diagnostic tests, obligate and corroborative features should be improved again [25] (Table 2). The development of high-field magnetic resonance imaging (MRI) in the 80-ties was a significant milestone in the further studies of NBIA. Brain MRI allowed for noninvasive demonstration of decreased T2 relaxation time caused by iron deposition, what correlates with iron accumulation of the brain in postmortem studies. Thus, MRI has become a highly sensitive diagnostic tool for the diagnosis of NBIA [26]. An ''eye of the tiger'' sign, first described by Sethi et al. in 1988 is a specific MRI pattern, a key diagnostic feature of PKAN [27]. It is high signal intensity in the center of the globus pallidus interna with low signal intensity in the surrounding region. The surrounding hypointensity of the globus pallidus represents excess iron deposition and the central hyperintensity is

Table 2 – Diagnostic criteria for PKAN proposed by Swaiman and Dooling et al. [22–24].

Obligate features	Corroborative features
Onset in the first three decades	Corticospinal tract involvement
Progression of signs and symptoms	Progressive intellectual impairment
Evidence of extrapyramidal dysfunction (dystonia, rigidity, tremor, bradykinesia, choreoathetosis)	Retinitis pigmentosa, optic atrophy
T2-weighted brain MRI: high signal intensity in the center of the globus pallidus interna with low signal intensity in the surrounding region (eye of the tiger sign)	Family history of similar disorder

due to necrosis and edema [28]. What is important, MRI changes may precede clinical onset [29]. In the early stages of PKAN only isolated high signal intensity on T2-weighted images of the globus pallidus interna can be observed [26]. Hayflick et al. emphasized that there is an absolute correlation between ''eye of the tiger'' sign and presence of mutations in *PANK2* [1,30]. However, similar changes in MRI were described in many other conditions and these should be taken into consideration in the differential diagnosis, when appropriate (Fig. 1). This characteristic pattern was also observed in neuroferritinopathy. However, in these cases the involvement of other basal ganglia nuclei (caudate and putamen), thalamus and cerebral cortex was found and it is not seen in PKAN [31]. Moreover, ''eye of the tiger'' can be seen in non-NBIA conditions such as corticobasal degeneration [32], progressive supranuclear palsy [33] and multiple system atrophy [34]. Hypointensities of the globus pallidus, caudate nuclei, and putamen on T2 images have been described in beta-thalassanemia major [35], HIV infection [36], Wilson disease [37], toxic and metabolic degeneration [26]. Therefore, MR images should be scrutinized in the context of clinical data and other radiological findings. In later stages of the disease only hypointesity of the globus pallidus may be seen. This might be explained by further accumulation of iron deposits, which can obscure central hyperintensity [38]. Historically, all patients who had HSD/NBIA phenotype and radiological evidence of excess iron accumulation in the globus pallidus were diagnosed of PKAN. After the identification of mutations in the *PANK2* gene on chromosome 20p12.3–p13 the term pantothenate kinase-associated neurodegeneration (PKAN) has been proposed only for patients with confirmed or suspected mutations in *PANK2*. For the remainder the term ''neurodegeneration with brain iron accumulation'' has been suggested [1]. Mutations (mainly missense) as well as deletions, duplications and splice-site ones have been detected in all seven exons of *PANK2* [39]. Mutations in *PANK2* occur in all cases of classic PKAN, especially in those with ''eye of the tiger sign'' on brain MR and around one third of cases with atypical features [1]. While mutations in patients with classic disease usually lead to protein truncation, those in atypical patients often result in amino acid changes. It indicates that many of patients with atypical form of disease may have a residual panthotenate kinase 2 activity [1]. Two most frequent mutations (1231G > A, 1253C > T) account for about one third of all cases and the majority of the remaining carry ''private mutations'' [30]. It is noteworthy that G411R mutation was detected on only one chromosome in few cases. It suggests that G411R might act in semidominant fashion, with one allele sufficient to cause disease [1].

Transcranial sonography revealed bilateral hyperechogenicity restricted to the globus pallidus and substantia nigra (SN), what correlates with the hypointense regions detected during MR examinations [40]. Dopamine transporter (DaT) and cardiac 123I-meta-iodobenzylguanidine (MIBG) SPECT imaging are generally within normal limits [41,42]. A recent neuropathological study in 6 genetically confirmed cases of PKAN demonstrates that mainly central nervous system is occupied with occasional peripheral manifestations of the disease, i.e. testicular pathology, lipid profile abnormalities, acanthocytosis.

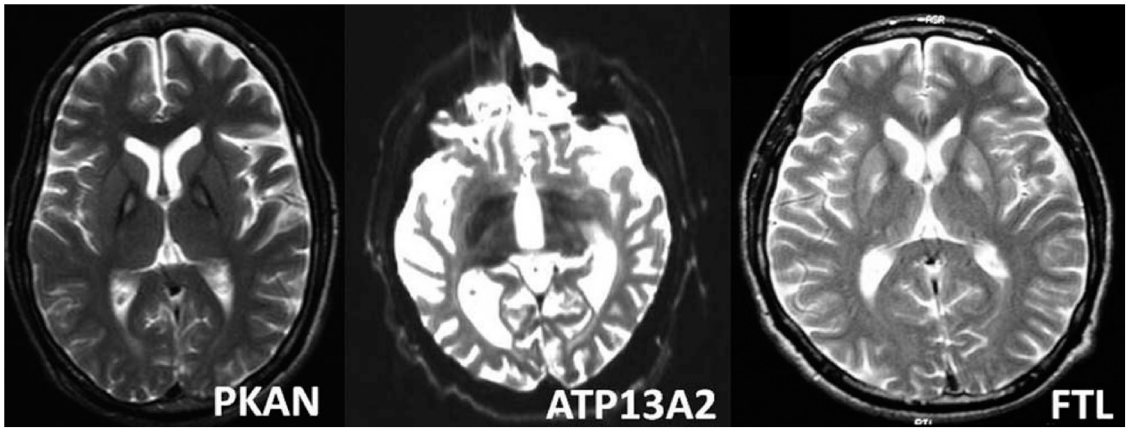

Fig. 1 – Examples of brain MR imaging in NBIA disorders. On the left, pantothenate kinase-associated neurodegeneration (PKAN), in the middle, Kufor-Rakeb disease (due to ATP13A2 mutations), and neuroferritinopathy (due to FTL mutations) on the right. In PKAN there is a classic eye-of the-tiger sign. Iron accumulation affected the putamen and caudate in our Kufor-Rakeb disease patient. In this gene-proven neuroferritinopathy patient, there was iron deposition in the basal ganglia, with a slight hint of thalamic involvement.
Image reprinted with permission from John Wiley and Sons: Schneider et al. [2].

Pathological changes predominantly affected globus pallidus, but adjacent structures (medial putamen, internal capsule) and subcortical white matter also could be involved. The most prominent microscopical finding includes iron deposition, neuronal degeneration and the presence of widely disseminated, rounded or oval structures termed spheroids. Two types of spheroids have been distinguished: smaller, eosinophilic spheroidal structures as a substrate of dystrophic neurons; and larger, reflecting degenerating neurons. Iron accumulation was observed in the globus pallidus within the cytoplasm of neurons, glia and macrophages, especially in a perivascular distribution. Increased diffusely in the neuropil of the globus pallidus ('iron dust') was also present [43]. Numerous previous articles reported that PKAN could be characterized as both synucleinopathy and tautopathy. However, Kruer et al. in the recent studies performed in gene-proven patients have not confirmed presence of Lewy bodies, neurofibrillary tangles and tau-positive neuritis [43]. This discrepancy could result from the fact that many histological studies were performed before identification of the *PANK2* gene. Thus, it is possible that some of the historical ''Hallervorden–Spatz disease'' cases with Lewy body pathology may actually not have had PKAN, but at least another form of NBIA [43]. In the latest study Li et al. also confirmed that PKAN is not synucleinopathy, however described one autopsy case of significant tau pathology comprising neurofibrillary tangles and neuropil threads [44]. The treatment for NBIA disorders is challenging and requires a comprehensive approach to the patients. However, it still remains symptomatic. Most NBIA patients do not respond well to levodopa administration. However, in reducing abnormal movements and spasticity several drugs may be efficacious, including benzodiazepines, anticholinergics, baclofen, typical and atypical neuroleptics, botulinum toxin injection and intrathecal baclofen [30]. Deep brain stimulation (DBS) of the internal globus pallidus may produce some benefit, especially in the patients with PKAN, but results are variable [45,46]. Supplementing of pantothenic acid seemed to be effective in drosophila models of PKAN, but results for human trials are not yet available [47].

4. PLA2G6-associated neurodegeneration (PLAN) – NBIA Type 2

PLA2G6-Associated Neurodegeneration (PLAN) is a result of mutations in the *PLA2G6* gene, which encodes a calcium-independent phospholipase A2 (iPLA2-VIa) [48]. Phospholipase A2 enzymes catalyze the hydrolysis of glycerophospholipids, generating a free fatty acid (mainly arachidonic acid) and a lysophospholipid, which are thought to play a crucial role in cell membrane homeostasis, signal transduction, cell proliferation and apoptosis. Thereby defects in iPLA2-VIa cause cellular membrane abnormalities which lead to pathological changes and eventually culminating in progressive neurological impairment [49].

Depending on age two clinical phenotypes can be distinguished- infantile neuroaxonal dystrophy (INAD) and atypical neuroaxonal dystrophy (atypical NAD). INAD usually occurs before the lapse of 2 years and progressive psychomotor decline is the most frequent presentation. Characteristic features also include cerebellar ataxia, gait impairment, visual disturbances due to optic atrophy, truncal hypotonia and pyramidal signs. Fast rhythms on an EEG and general seizures may, also, be present [1]. The clinical spectrum of late-onset PLAN is not as well characterized and includes progressive dystonia, parkinsonism, cognitive impairment, psychiatric features and optic atrophy [50]. Karak syndrome described by Mubaidin et al. as a novel degenerative disorder of the basal ganglia and cerebellum [51] has been shown to be caused by mutations in *PLA2G6* and falls into the spectrum of atypical NAD [48]. In the early stage of INAD neuroimaging shows cerebellar atrophy. T2-weighted MR demonstrates hypointensity of globus pallidus, dentate nuclei, and substantia nigra, which reflects iron depositions [31]. However, iron accumulation may be absent, and MRI can be even normal. In addition, cortical atrophy and white matter changes can also occur [50]. Pathological studies demonstrated neuroaxonal dystrophy, alpha-synuclein pathology with Lewy bodies and Lewy neurites. Lewy body pathology was particularly severe in the neocortex, basal forebrain, hippocampal formation and brainstem nuclei. The findings of Lewy body pathology in PLA2G6 strenghten a link with other neurodegenerative diseases such as Parkinson's disease and dementia with Lewy bodies. Cerebellar atrophy may be present and with iron accumulation in the globus pallidus is highly specific for INAD. The accumulation of hyperphosphorylated tau also been reported [52,53].

5. Aceruloplasminemia (aCP)

Aceruloplasminemia (aCP) is an autosomal recessive disorder caused by mutations in the ceruloplasmin gene (*CP*), on chromosome 3q [54,55]. Ceruloplasmin plays an essential role in the mobilization of iron from tissues through its ferroxidase activity and carries 95% of plasma copper. Protein dysfunction resulted in excessive iron accumulation in the brain (basal ganglia, nuclei, thalami, dentate nuclei and cerebral and cerebellar cortices), liver and pancreas [56]. The classical triad of aCP include young-adult onset diabetes mellitus, retinal degeneration and various neurological symptoms [54]. Mean-onset age is around 50, with prominent extrapyramidal features and cognitive impairment. Cerebellar ataxia is also frequent sign [55]. Laboratory findings typically reveal undetectable ceruloplasmin in the serum, low levels of serum copper and iron and elevated serum ferritin [31]. T2-weighted brain MRI scans showed widespread hypointensity in the cerebral cortex, globus pallidus, putamen, caudate, thalamus, dentates, substantia nigra, and cerebellar cortex [31]. Treatment for aCP remains symptomatic. Several studies have reported positive results of treating aceruloplasminemia with iron-chelating agents such as desferrioxamine mesylate [57] and deferasirox [55]. Administration of an anti-oxidative drugs like deferiprone has also been suggested. However, systematic studies are needed to assess the efficacy of these therapies [58].

6. Neuroferritinopathy

Neuroferritinopathy (also known as hereditary ferritinopathy) is a result of ferritin light chain (*FTL*) gene mutations. In

contrast to the other NBIA disorders, inheritance is autosomal dominant. Onset begins around the age of 40. The clinical presentation is characterized by extrapyramidal features including chorea and dystonia [59]. MRI may reveal consistent involvement of the dentate nuclei, globus pallidus, and putamen, with areas of hyperintensity due to probable cavitation, involving the pallida and putamen [31]. Laboratory tests show decreased level of serum ferritin. Pathology assessment shows severe neuronal loss in the basal ganglia, atrophy of cerebellum and cerebral cortex, abnormal iron accumulation and the presence of ferritin inclusion bodies (IBs) in neurons and glia [60]. Ferritin IBs can also be seen in hepatocytes, cells of the renal tubular epithelium, endothelial cells of capillaries, and skin fibroblasts [61,62]. Effective treatment still remains unknown. Focal botulin toxin injections and oral antioxidant therapy can be beneficial, but this approach requires further studies [63].

7. FA2H-associated neurodegeneration (FAHN)/SPG35

Autosomal recessive FA2H-Associated Neurodegeneration (FAHN) results from the mutations in the fatty acid hydroxylase gene, *FA2H* [64]. FA2H plays a role in the metabolism of myelin sheaths [65]. It produces free 2-hydroxy fatty acids necessary for the biosynthesis of ceramide, galactosylceramide and sulfatide, which are major constituents of normal CNS myelin [66]. Mutations in the *FA2H* gene had previously been associated with progressive familial leukodystrophy and hereditary spastic paraplegia (SPG35). The clinical phenotype is characterized by childhood- onset gait impairment with prominent spastic quadriplegia, pyramidal tract signs, profound ataxia and dystonia. Moreover, optic atrophy, nystagmus, acquired strabismus and seizures may be present. In general, clinical presentation discussed above demonstrated similar features to those observed in neuroaxonal dystrophy (NAD) [64]. T2-weighted MR shows bilateral hypointensities of the globus pallidus compatible with excess iron deposits, prominent pontocerebellar atrophy, mild generalized cortical atrophy, thin corpus callosum and confluent periventricular white matter T2 hyperintensities [64]. It is noteworthy that white matter abnormalities are hallmark feature of leukodystrophies and thin corpus callosum is a core element of some types of hereditary spastic paraplegia [67]. Deterioration of lipid and ceramide metabolism caused by FA2H deficiency is the common pathologic mechanism of NBIA, HSP and leukodystrophies. Thus, the clinical and radiological overlap between these diseases is not surprising. Overall, *FA2H* mutations result in a clinical spectrum rather than distinct disorders [68]. Neuropathological studies are still awaited.

8. Kufor-Rakeb disease (PARK9)

Kufor-Rakeb disease is an autosomal recessive extrapyramidal-pyramidal syndrome, originally described in the consanguineous Jordanian family from the village Kufor-Rakeb [69]. It is caused by mutations in *ATP13A2* gene [70], which is localized on chromosome 1p36 [71]. *ATP13A2* encodes a lysosomal 5 P-type ATPase and in the human brain, it is localized on pyramidal neurons within cerebral cortex and dopaminergic neurons in the substantia nigra [72]. In the recent study Park et al. demonstrated several different mechanisms by which mutations in *ATP13A2* may contribute to the development of Kufor-Rakeb disease. First, mutant ATP13A2 can lead to impaired lysosomal function and this effect may result in the cellular accumulation of toxic and unnecessary proteins such as α-synuclein. Moreover, the mutant proteins are degraded by proteasomal, not the lysosomal pathway. It might overload proteasomal pathway and handicap its normal function to degrade other proteins, particularly if the lysosomal pathways are not working efficiently. The third mechanism includes impaired ion transportation or ionic imbalance that results in increased oxidative stress in the cell [73]. Characteristic clinical features include juvenile-onset, levodopa-responsive parkinsonism, pyramidal dysfunction and eye movements abnormalities with supranuclear gaze palsy. Slowing of vertical and horizontal saccades and saccadic pursuit may be present [74]. A good response to levodopa is transient and levodopa-dyskinesias tend to develop early [75]. Cognitive deterioration and overt dementia have been described [70]. Brain MR images reveal generalized brain atrophy affecting both cerebral and subcortical structures and hypointensities of the putamen and caudate nuclei, reflecting iron deposition, however neuropathological confirmation is still awaiting [76]. Dopamine transporter imaging demonstrated bilateral symmetrical reduction of striatal activity indicative of diminished presynaptic function. Transcranial sonography of the SN remained within normal limits. Electrophysiological studies showed pyramidal tract damage [77].

9. Mitochondrial membrane protein associated neurodegeneration (MPAN)

Extensive studies led to identification of a new mutation causing a neurodegeneration with brain iron accumulation. Hartig et al. described a Polish cohort whose clinical phenotype was characterized by progressive spasticity, dystonia, optic atrophy, motor axonal neuropathy, and psychiatric signs. T2-weight MR showed bilateral hypointensity of the globus pallidus and substantia nigra. A histopathological examination in a single autopsy case detected Lewy bodies, tangles, spheroids, and tau pathology. Mutation in the gene *C19orf12* on chromosome 19 was revealed. The acronym MPAN (Mitochondrial Membrane Protein Associated Neurodegeneration) has been proposed [78].

10. Static encephalopathy of childhood with neurodegeneration in adulthood (SENDA syndrome)

Recently a static encephalopathy of childhood with neurodegeneration in adulthood (SENDA syndrome) was described. Genetic cause is still unknown. The clinical presentation is characterized by early onset spastic paraplegia and cognitive impairment which remains static until the late 20s to early 30s but then progresses to parkinsonism and dystonia. Moreover,

sleep disorders, frontal release signs, eye movement abnormalities and dysautonomia may be present. Brain MRI revealed iron accumulation in the globus pallidus, hypointensities in the substantia nigra and white matter changes. A good response to levodopa was noticed [79].

11. Conclusions

We have summarized the major genetic causes and clinical heterogeneity of NBIA. It is worth pointing out that considerable developments in the field of neurodegenerative disorders are being witnessed. However, the exact pathophysiology of NBIA is still poorly understood. In order to develop new therapies, which still remain symptomatic and often unsatisfactory, it is crucial to better understand the pathologic mechanism, clinical course and diagnostic criteria of the distinct NBIA syndromes.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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