

Pantothenate Kinase-Associated Neurodegeneration

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Abstract: Pantothenate kinase-associated neurodegeneration (PKAN) is a hereditary progressive disorder and the most frequent form of neurodegeneration with brain iron accumulation (NBIA). PKAN patients present with a progressive movement disorder, dysarthria, cognitive impairment and retinitis pigmentosa. In magnetic resonance imaging, PKAN patients exhibit the pathognomonic “eye of the tiger” sign in the globus pallidus which corresponds to iron accumulation and gliosis as shown in neuropathological examinations. The discovery of the disease causing mutations in *PANK2* has linked the disorder to coenzyme A (CoA) metabolism. *PANK2* is the only one out of four PANK genes encoding an isoform which localizes to mitochondria. At least two other NBIA genes (*PLA2G6*, *C19orf12*) encode proteins that share with *PANK2* a mitochondrial localization and all are suggested to play a role in lipid homeostasis.

With no causal therapy available for PKAN until now, only symptomatic treatment is possible. A multi-centre retrospective study with bilateral pallidal deep brain stimulation in patients with NBIA revealed a significant improvement of dystonia. Recently, studies in the PANK *Drosophila* model “fumble” revealed improvement by the compound pantethine which is hypothesized to feed an alternate CoA biosynthesis pathway. In addition, pilot studies with the iron chelator deferiprone that crosses the blood brain barrier showed a good safety profile and some indication of efficacy. An adequately powered randomized clinical trial will start in 2012.

This review summarizes clinical presentation, neuropathology and pathogenesis of PKAN.

Keywords: *PANK2*, CoA, iron, neurodegeneration, lipid metabolism, mitochondria, NBIA.

INTRODUCTION

The heterogeneous group of disorders named neurodegeneration with brain iron accumulation (NBIA) shares the feature of iron deposits in basal ganglia which are detectable by magnetic resonance imaging (MRI). The condition was previously known as Hallervorden-Spatz-Syndrome but the name was abandoned because of unethical activities of these authors in Nazi Germany.

Our understanding of the genetic basis of NBIA has evolved significantly since the identification of *PANK2* in 2001 [1]. Autosomal recessive mutations in *PANK2* cause pantothenate kinase-associated neurodegeneration which comprises about 50 % of NBIA cases [2, 3]. The prevalence is about one to three in 1,000,000 [4]. Pantothenate kinases are the rate limiting enzymes in the coenzyme A (CoA) biosynthesis pathway and subcellular localization experiments of *PANK2* link this pathway to mitochondria [5]. Since the identification of *PANK2*, a number of studies have sought to understand the biological role of this enzyme with the aim of advancing treatment of PKAN patients. Even so, only symptomatic treatment is available for PKAN patients so far.

Accumulation of iron in the basal ganglia has provided a pathophysiological overlap between NBIA and common

neurodegenerative diseases like Parkinson (PD) disease [6]. Iron was also identified to be part of amyloid plaques in brain of patients with Alzheimer Disease (AD) [7]. Increased iron levels in brain have been shown to enhance A β toxicity in a *Drosophila* model [8]. Up to now, seven further genes (*PLA2G6*, *FTL*, *CP*, *FA2H*, *ATP13A2*, *C2orf37*, *C19orf12*) have been linked to NBIA [9-18]. Mutations in two of them (*PLA2G6*, *C19orf12*) have been identified in patients with idiopathic Parkinson disease underscoring the commonalities between PD and NBIA at the molecular level [19,12].

In this review we summarize the current understanding of *PANK2* dysfunction and clinical manifestations in PKAN.

CLINICAL PHENOTYPE

Classic PKAN starts in the first decade, usually before age six years. The first symptom is in most instances a gait abnormality. Progressive dystonia is the cardinal symptom of PKAN, and involves primarily the cranial region and the limbs. Dysarthria is another common symptom. Pyramidal tract involvement is also common and may manifest as spasticity, hyperreflexia, and extensor toe signs. Developmental delay beyond motor signs is occasionally encountered, and cognitive impairment correlates with age of onset [20]. Pigmentary retinal degeneration occurs in two-thirds of patients leading to night blindness followed by progressive loss of peripheral visual fields. Optic atrophy, in contrast, and epileptic seizures are rare [21]. In most cases, the disease progresses relentlessly, but the rate of progression does not cor-

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relate in general with age of onset [3]. Most patients with classic PKAN are wheelchair-bound by age 15 years. Premature death is mostly due to secondary complications (most prominently, aspiration pneumonia following dysphagia) but with improved care a number of patients live now into adulthood.

Approximately 25% of affected individuals have an age of onset later than 10 years (atypical presentation) with a more gradual progression of disease. Speech problems including dysarthria, palilalia and tachylalia may be the presenting feature of patients with atypical PKAN. While later onset correlates with less cognitive impairment [20], psychiatric signs including impulsivity, aggression, depression, emotional lability, and tics are more prevalent [22].

HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration) is now considered part of the PKAN disease spectrum since mutations in the *PANK2* gene have been identified in the only two reported HARP families [23].

IMAGING

Iron deposits in brain cause local magnetic field inhomogeneities with decreased T2 relaxation time and therefore appear hypointense (dark signal) on T2- and T2*-weighted magnetic resonance imaging (MRI). Importantly, studies of healthy volunteers and Parkinson patients have shown a linear relationship between MRI findings and brain iron concentrations from post mortem studies [24]. While all NBIA forms show the eponymous brain iron, the PKAN MRI is kind of pathognomonic since it shows the “eye of the tiger” sign (Fig. 1). The resemblance is due to a central region of hyperintensity (gliosis) in the center of the hypointense iron accumulation in the globus pallidus [2, 3, 25]. Until now, almost all individuals with *PANK2* mutations have the “eye of the tiger” sign, and almost all individuals with the sign carry *PANK2* mutations [25-27]. The MRI changes occur early in the course of the disease and have already been used to predict PKAN in presymptomatic sibs of affected individuals [28].

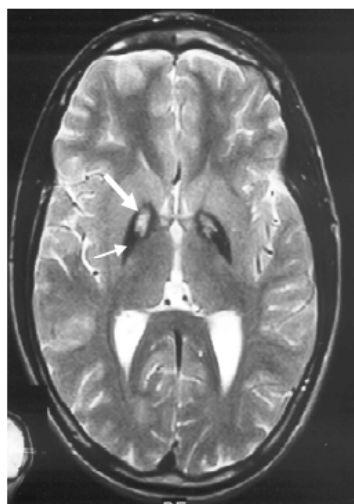


Fig. (1). Axial T2-weighted magnetic resonance images of a PKAN patient. Hypointensity is marked by the thin arrow, the high signal intensity foci in the anteromedial region by the thick arrow (image were kindly contributed by Tomasz Kmiec).

Susceptibility-weighted MRI demonstrates involvement of nigropallidal pathways [29]. Multiple system atrophy and cortical basal ganglionic degeneration may exhibit similar lesion, but clearly differ in clinical course or other imaging features [30, 31].

TREATMENT

Until now, there is no specific treatment for PKAN. Oral or intrathecal baclofen, stereotactic pallidotomy and anticholinergic treatment may provide symptomatic relief but have no known disease-modifying effects [32, 33].

Iron chelators which cross the blood brain barrier are an obvious option for pathophysiologically founded treatment. Treatment with deferiprone led to radiological and clinical improvement in two idiopathic NBIA patients [34, 35]. An unblinded, single-arm pilot study of deferiprone in 10 PKAN patients showed good tolerability and significant median reduction of globus pallidus iron of 30% ($p=0.008$) after 6 months treatment, but no change in clinical scores [36]. Another unblinded, single-arm pilot study in NBIA including four PKAN cases underlined the safety and tolerability of deferiprone, and revealed mild-to-moderate clinical improvement in 2 of the 4 PKAN patients [37]. These results warrant a large, adequately powered, randomized, double-blind trial which will start in 2012. The trial is conducted by an international consortium (TIRCON: Treat Iron-Related Childhood-Onset Neurodegeneration) including the authors and funded by the European Union.

While iron chelation represents the most feasible and promising candidate therapy for NBIA today, it remains unclear to what extent iron removal affects the phenotype. A treatment in PKAN that targets the primary defect may be pantethine which acts as an alternative precursor for CoA synthesis bypassing *PANK2*, the defective enzyme in PKAN. In *E. coli* a pantothenate kinase phosphorylates both pantothenate and pantethine [38]. In a *Drosophila* model pantethine treatment led to rescue of neurodegeneration and increase in life span which argues for an alternative kinase or pathway for pantothenate metabolism in the fly and possibly in human [39].

Finally, in view of the oxidative stress in NBIA that is presumably triggered by iron via the Fenton reaction, treatment with antioxidants may be an option but this has not been evaluated so far neither *in vitro* nor *in vivo*.

PANTOTHENATE KINASE AND COA BIOSYNTHESIS

The phosphorylation of pantothenate (Vitamin B5) represents the first and crucial (rate-limiting) step of CoA biosynthesis (Fig. 2). The other four steps which all take place in the cytosole are catalyzed by PPCS, PPCDC and the bifunctional enzyme PPAT-DPCK. CoA is a crucial coenzyme of a large number of oxidative and synthetic enzymes, in pathways like the citric acid cycle, sterol biosynthesis, amino acid metabolism, fatty acid biosynthesis and oxidation.

The human genome contains four genes which encode active pantothenate phosphorylating enzymes. These enzymes belonging to the pantothenate kinase family contain a highly conserved catalytic domain (approx. 83% identical)

but differ in the N-terminus which probably serves regulating purposes [40, 41]. PANK1 and PANK3 are cytoplasmic enzymes. A fourth related enzyme (PANK4) misses one Glu/Asp in its catalytic domain, in addition it harbours a carboxy-terminal domain with unknown function (COG1578 superfamily of unknown function, aa 450-733) [5]. Although *in vitro* data suggested an absence of kinase activity, the successful complementation of *Drosophila* and *E. coli* mutants confirmed its PANK activity [5, 42].

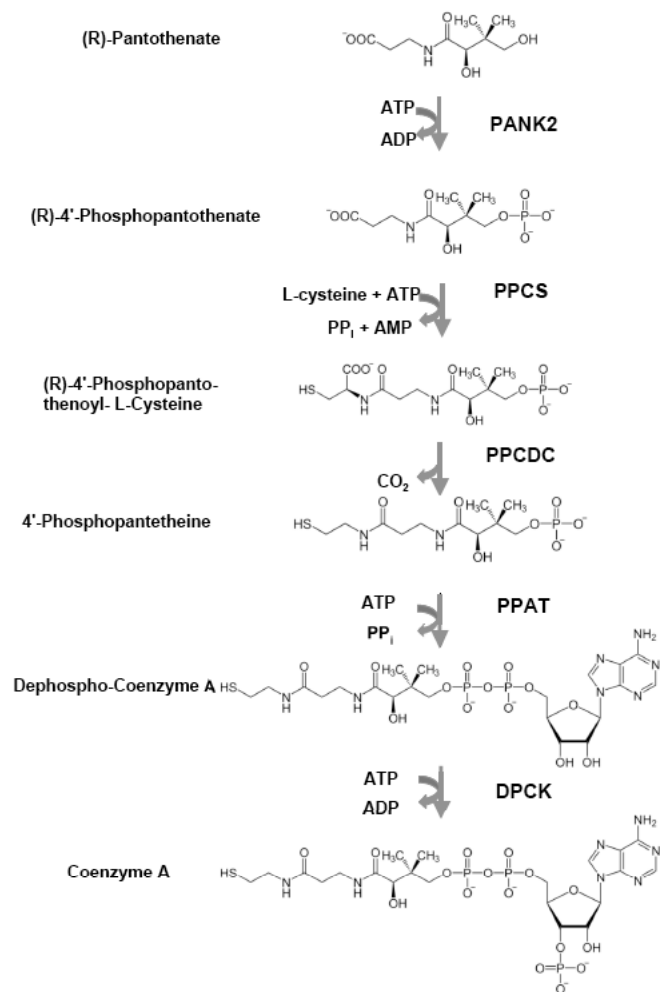


Fig. (2). CoA biosynthesis route.

For PANK1alpha and PANK3 the crystal structure is available [41]. Both pantothenate kinases are part of the actin fold protein kinase superfamily. They consist of two domains (A and B), the B-domain contains a dimerization-interphase conferring a homodimer-configuration and an acetyl-CoA-binding-motif. Via acetyl-CoA-binding, ATP-binding is inhibited [43]. Thereby the activity of the pantothenate kinases is regulated by intracellular CoA levels which create a feedback regulation mechanism. On the other side, the presence of palmitoylcarnitine inhibits acetyl-CoA inhibition, thereby activating *PANK2* [43].

The 63kDa precursor of *PANK2* comprises in addition to the highly conserved catalytic domain a mitochondrial targeting signal [5, 44]. Via a 59kDa intermediate it is processed in two steps in the mitochondrial matrix by the mitochondrial processing peptidases (MPP) to a final 48 kDa

PANK2, suggesting an intramitochondrial localization, in the intermembrane space or in the matrix. One argument in favour of an IMS localization is the fact that other proteins that also have two MPP binding sites are found in the IMS [43], together with the cytoplasmic localization of the other enzymes involved in the CoA biosynthesis. Via porin, an abundant membrane protein, 4'-phosphopantothenate might be transported into the cytosol in order to serve the downstream pathway.

A shorter *PANK2* isoform (288 aa) formed by an alternative exon 1 (1a) does not have a mitochondrial targeting signal [5]. Since no disease-causing mutation in exon 1a has been identified so far, the relevance of this isoform remains unclear.

Complementation experiments and *in vitro* enzymatic assays confirm kinase activity of *PANK2* [3, 44]. Increased pantothenate serum levels have been measured in PKAN patients [45]. This finding argues in favour of pantothenate being the physiological substrate. Due to its ability to sense acetyl-CoA and palmitoylcarnitine levels, *PANK2* might also function as a sensor of the mitochondrial demand for CoA [43].

GENETICS

Autosomal recessive mutations in *PANK2* have been implicated with PKAN appearance. *PANK2* spans 35kB of genomic DNA and contains 8 exons with alternate usage of exon 1a and 1b [5]. According to the human gene mutation database in Cardiff (<http://www.hgmd.org/>) more than 100 mutations, including small deletions, duplications, missense mutations and splice site mutations have been identified. Hayflick *et al.* reported that about 10% of patients carry only one mutation and discussed the potential role of promoter mutations [21, 46]. In about 5% (3/34) of cases exonic deletions were detected in European samples and so far no cases with only a single mutated allele [3]. Two different nomenclatures for mutations have been used in the literature based on different predicted translation initiation codons. We use the longer transcript (NM_153638) preceding the other one by 110 amino acids (330 nucleotides). The mutations are evenly distributed throughout the conserved parts of the *PANK2* gene [2, 3]. Most of the known mutations are private mutations. Hayflick *et al.* reported that two common mutations (c.1561G>A, p.G521R and c.1583G>A, p.T528M) account for 33% (41/123) of all PKAN alleles [2]. A 1-bp-deletion (c.573delC, p.S191RfsX13) was frequently identified in patients from Poland which might be due to a founder effect [3]. Presence of null-mutations on both alleles strongly correlates with an early onset (younger than six years). *In vitro* cell culture assays have been performed to test *PANK2* activity of different *PANK2* alleles with the purpose of correlating disease severity to the level of pantothenate kinase activity. Some mutations like c.1561G>A, p.G521R lead to a loss of kinase activity. Crystallographic mapping by Hong *et al.* revealed that the c.1561G>A, p.G521R mutation affects the ATP binding site [41]. Correspondingly, this mutation leads to early onset. Other mutations result in only slightly reduced *PANK2* activity. The mutation c.1583G>A, p.T528M which is located on the surface of *PANK2* shows no discernible change of enzyme activity [44], but has a

moderate effect on *PANK2* stability and slightly reduced *PANK2* activity in an *E. coli* experiment [3, 41]. Such mutations are associated with late onset when homozygous or compound heterozygous.

TRANSGENIC ANIMALS

As in human, the murine genome encodes four pantothenate kinases. However, unlike human *PANK2*, mouse *Pank2* localizes to cytosole [47]. The difference in the sub-cellular localization is also reflected in a different phenotype. Mice with homozygous null mutations in *Pank2* develop weight loss, retinal degeneration and infertility, but no neurological symptoms such as dystonia and no accumulation of iron in the central nervous system [48]. When challenged with a vitamin B5 deficient diet, wild type mice develop azoospermia, a low-lying pelvis and slow steps [49].

Human *PANK2* is ubiquitously expressed with a high rate of expression in brain tissue, especially cerebellum and caudate nucleus. Murine *Pank2* on the other hand, has a low expression in brain and a very high testicular expression [47]. The attenuated phenotype in mice might be explained by the specific expression patterns of *Pank2* in mice.

The fly genome contains only one pantothenate kinase gene (*fumble*, *fbl*), which codes for five isoforms. One of those five isoforms localizes to mitochondria. *Drosophila* flies with a hypomorph *fbl*-allele show reduced pantothenate kinase activity, sterility in both sexes, movement disorders and neurodegeneration. Deaths usually occur in pupae stage or after eclosion. Electron microscopy shows swollen mitochondria and destroyed cristae and membranes. Introduction of human *PANK3* and *PANK4* which are both cytosolic enzymes in the *fumble* fly failed to completely reverse the phenotype which points to the relevance of a mitochondrial localized pantothenate kinase activity [42].

Rana and colleagues suggested that pantethine might work as a substrate for a *PANK2* independent CoA biosynthesis. Treatment with pantethine restored all phenotypes in the dPANK/*fumble* fly including CoA deficiencies, neurological dysfunction and mitochondrial discrepancies [39]. Based on this promising finding, the therapeutical effectiveness of pantheteine is currently tested in mice.

PATHOLOGY

Most of the neuropathologic literature on NBIA is from a pre-molecular era making it difficult to draw firm conclusions on PKAN pathology. However, typical cases with the diagnosis Hallervorden-Spatz syndrome are likely to correspond to PKAN. Early autopsy cases were characterized by rust-brown pigmentation in the globus pallidus and the reticular zone of the substantia nigra, with iron being the major component of this pigment [50]. While these areas contain approximately three times the normal amount of iron, a global increase in brain iron is not seen and systemic iron metabolism is normal. In PKAN, spheroid bodies (thought to represent swollen axons) have been observed in the pallidonigral system as well as in the white and gray matter of the cerebrum [51]. Spheroid bodies in the peripheral nervous system, in contrast, point to the diagnosis of infantile neuroaxonal dystrophy (INAD, previously Seitelberger's dis-

ease) which is due to mutations in the phospholipase A2, group VI (*PLA2G6*) gene. In a recent study, Kruer *et al.* described neuropathological findings in six cases of molecularly confirmed PKAN [44, 52]. In contrast to INAD pathology, the PKAN pathology was restricted to the globus pallidus. Apart from iron and gliosis in the globus pallidus which corresponds to the radiological "eye of the tiger" sign, several distinctive features of PKAN pathology were found. Notably, Lewy bodies and other alpha-synuclein abnormalities were not encountered arguing against earlier perceptions of PKAN as a synucleinopathy. Similarly, neurofibrillary tangles and tau-positive neurites were also absent. In contrast, both tau-positive neuritis and Lewy bodies have been described in patients with *C19orf12* mutations [12]. Iron-laden macrophages were prominent in all PKAN cases, which may indicate an attempt to remove iron from the brain parenchyma. Intriguingly, increased amyloid precursor protein staining was found both in neuroaxonal spheroids and in neuronal processes. This finding may correspond to the recent recognition that amyloid precursor protein has a role in cellular iron efflux [53]. In addition, degenerating neurons were strongly positive for ubiquitin which points to accumulation of another abnormal and yet unassigned protein.

Obviously, the pathophysiological mechanisms underlying iron deposition in PKAN are of great interest considering the iron accumulation in more common neurodegenerative disorders, such as Alzheimer and Parkinson disease (PD).

While in PKAN the iron accumulation is located in globus pallidus, in PD the iron accumulation is detected in the substantia nigra. The pathological relevance of iron accumulation is supported by (i) the localization: iron changes are seen in the pars compacta of the substantia nigra which is the main site of pathogenesis in PD harbouring pigmented neurons which are involved in PD pathogenesis [54]. In comparison, age-related iron accumulation in normal controls occurs mainly in the pars reticulata in the substantia nigra [55-57]. Second, the correlation of iron accumulation with disease severity and motor score in the contralateral body side underlines its pathological relevance [58, 59]. However, disease duration is not correlated with iron accumulation in PD patients [60]. Interestingly, in patients with Alzheimer Disease, the development of parkinsonism is associated with accumulation of iron in the substantia nigra [61]. In principal, the hippocampus is the primarily affected site in Alzheimer Diseases [55, 62].

No nigral iron accumulation has been identified in pre-symptomatic PD or mild PD indicating that iron accumulation in PD may be a secondary phenomenon [63, 64]. On the contrary, in PKAN MRI changes have been found in pre-symptomatic individuals [28].

PATHOGENESIS

Neuroferritinopathy and aceruloplasminemia can be attributed directly to an impairment of proteins which are involved in iron metabolism [10, 11, 16, 18]. For the other NBIA disorders, the link from gene defect to iron accumulation is less clear.

Several hypotheses regarding the genesis of PKAN pathology have been discussed. The first concentrates on the

loss of the key enzyme of the biosynthesis of CoA. The resulting cellular CoA deficiency, which can be reproduced in the *Drosophila* and mammalian cell culture [39,65] may hamper beta-oxidation, thereby cellular energy and lipid metabolism since CoA serves as a key substrate for many cellular reactions.

Since the identification of further NBIA genes in the last three years, the role of lipid metabolism has received increasing attention in the pathogenesis of NBIA (Fig. 3). In addition, the mitochondria have taken centre stage following the verification of the mitochondrial localization of *PANK2*, *PLA2G6* and the recently identified *C19orf12* [5, 12, 66]. Although defects of the mitochondrial respiratory chain have not been identified in PKAN patients, elevation of lactate in plasma of a PKAN cohort compared to a control group point to mitochondrial dysfunction in PKAN patients [45]. In addition, defects in bile acid conjugation and lipid metabolism were shown in global metabolic profiling in fibroblasts of PKAN patients [45].

Insufficient remodeling and degeneration of mitochondrial inner membranes and presynaptic membranes has been shown in iPLA(2) β knock-out (KO) mice [67] and mitochondrial structure and function are impaired in dPANK/fbl mutants [39].

The *PLA2G6* gene encodes a calcium independent phospholipase [14] and leads to PLA2G6-associated neurodegeneration [14, 17]. *PLA2G6* is a crucial enzyme in membrane homeostasis, for instance by remodelling of membrane phospholipids [68]. Involvement of *PLA2G6* in cardiolipin metabolism has been shown in *Drosophila*. In eukaryotes, cardiolipin is exclusively found in the mitochondrial membrane and crucial for proper mitochondrial function [69]. Taffazin-deficient-*Drosophila*, a model of Barth syndrome, exhibit low cardiolipin concentration, abnormal cardiolipin fatty acyl composition, abnormal mitochondria, and poor

motor function [70-72]. This phenotype of the taffazin knockout is rescued by an additional inactivation of the *PLA2G6* gene.

Bras *et al.* suggested that *PANK2*, *PLA2G6* and Parkinson's Disease (PD) genes might be partners in a complex network of ceramide metabolism (Fig. 3). Ceramide metabolism has been linked to the pathogenesis of PD ever since heterozygous mutations in glucocerebrosidase (GBA) have been identified as a risk factor for PD [73, 74]. Galactosylceramide and sulfate are major components of myelin and play a critical role in its maintenance [75, 76]. Key substrate for generation of ceramide is CoA which establishes the link of ceramide metabolism to PKAN [77]. Involvement of *PLA2G6* in the ceramide pathway has been implicated since *PLA2G6* promotes ceramide generation via neutral sphingomyelinase-catalyzed hydrolysis of sphingomyelins [78].

Recently three further NBIA genes have been identified which can be linked to lipid and ceramide metabolism. Mutations in the *FA2H* gene have been identified in one subtype of NBIA named fatty acid hydroxylase-associated neurodegeneration (FAHN) [13]. *FA2H* encodes fatty acid 2-hydroxylase which is part of the ceramide biosynthesis due to its function to generate 2-hydroxylated fatty acids for integration in 2-hydroxydihydroceramide and 2-hydroxyceramide.

The *ATP13A2* gene is mutated in patients with Kufor-Rakeb syndrome which has recently been identified to be part of the NBIA spectrum [15]. *ATP13A2* mutations have been shown to cause a late onset neurodegenerative phenotype in dogs [79]. *ATP13A2* encodes a lysosomal divalent cation transporter [80]. Kruer *et al.* discussed that mutations in *ATP13A2* might lead to impaired membrane lipid recycling, and impaired autophagy and accentuated α -synuclein toxicity [13]. A recent study showed decreased ATP synthesis rates, increased mitochondrial DNA levels, a higher fre-

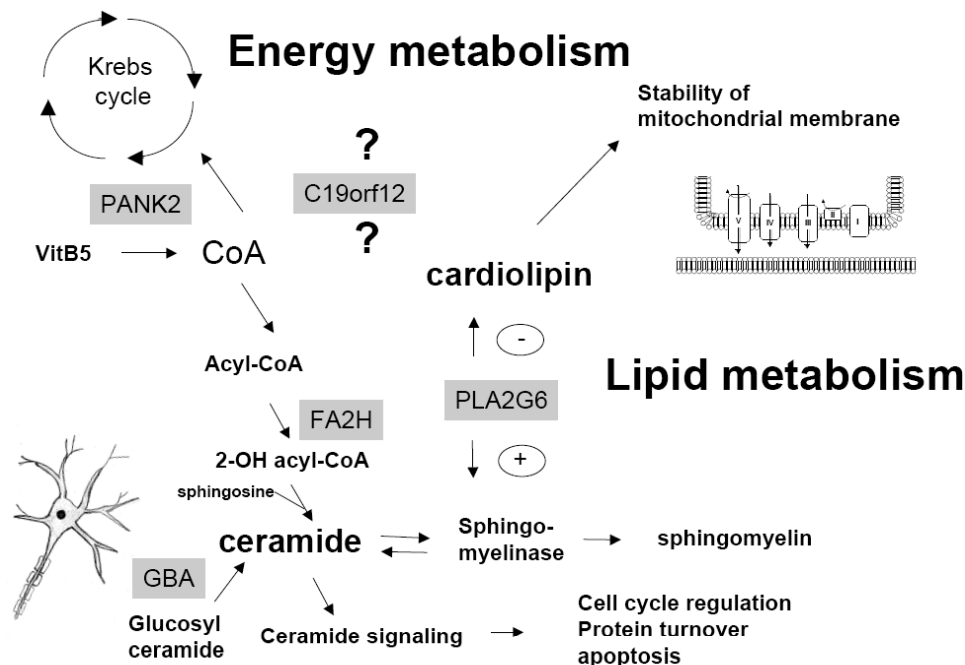


Fig. (3). Pathogenesis of NBIA: a schematic overview of interconnections of NBIA genes (adapted from Kruer *et al.* 2011).

quency of mitochondrial DNA lesions, increased oxygen consumption rates, and increased fragmentation of the mitochondrial network in fibroblasts from patients with *ATP13A2* mutations [81].

Mutations in *C19orf12* are the second frequent cause for NBIA after *PANK2*. The protein encoded by this orphan gene is localised to mitochondria and expression analysis in blood points to mitochondrial processes related to CoA [12].

As shown in (Fig. 3) the identification of further NBIA genes suggest impaired mitochondrial lipid metabolism as an important pathophysiological mechanism. Under certain circumstances impaired mitochondrial lipid metabolism is able to affect mitochondrial energy metabolism in a tissue specific manner as shown for the cardiolipin methyltransferase tafazzin and the acylglycerolkinase (AGK) [69, 82].

Another hypothesis concentrates on one of the most prominent gaps in NBIA research: the iron accumulation. It is still unknown whether iron accumulation is a primary trigger of PKAN pathogenesis or rather a pathogenic end product. Physiologically, there is an age related increase in iron content in the brain [56], primarily in the globus pallidus, red nucleus, substantia nigra pars reticulata, dentate nucleus, and putamen. In the developing brain, iron is especially high in oligodendrocytes and is probably needed for the high energy demands of myelin synthesis [83]. Restriction of iron in diet leads to hypomyelination in rat models [84, 85]. Via iron accumulation in macrophages iron is delivered to maturing oligodendroglial progenitors in the process of oligodendrogenesis [86]. Iron accumulation in NBIA might be a consequence of disturbance of lipid metabolism and consequently myelin breakdown and increased myelin turnover [87].

In the second step of the CoA pathway cysteine is incorporated into 4'-phosphopantothenic acid. It was discussed that deficiency of *PANK2* activity may lead to accumulation of cysteine and subsequently iron due to chelation [1,88]. Autooxidation in the presence of iron leads to the generation of free radicals. Involvement of oxidative stress in PKAN pathogenesis has been shown in the *Drosophila*. dPPCS and dPANK/fbl-*Drosophila*-mutants but not PPAT-DPCK-mutants are hypersensitive to cysteine. Additionally, overexpression of ROS scavengers resulted in a protective effect against cysteine induced lethality in this model [89].

One of the remaining questions is why an alteration of a ubiquitously expressed gene like *PANK2* results in an isolated brain disorder. The neurological phenotype of PKAN might be explained by (i) the pronounced sensitivity of the brain in particular the basal ganglia to oxidative stress added by the high energy demand and by the physiological high iron content of this organ [90] and by (ii) the specific high *PANK2* expression levels in brain which accounts for 45% of PANK activity.

CONCLUSION

Though our understanding of etiology and phenotype of PKAN has greatly improved, the precise pathomechanisms leading from the gene defect to the clinical manifestations are still a matter of debate. The challenge in the future will be to unravel the exact function of *PANK2* and its interaction with the other NBIA genes. A better understanding of these

processes may open novel avenues for further therapeutic research in NBIA patients. As we gain more understanding of NBIA pathogenesis, we might advance our knowledge about more common neurodegenerative disorders like Parkinsons and Alzheimers Disease.

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CONFLICT OF INTEREST

None declared.

ABBREVIATION

| | | |
|-------|---|---|
| PKAN | = | Pantothenate kinase-associated neurodegeneration |
| NBIA | = | Neurodegeneration with brain iron accumulation |
| PPCS | = | 4'-phosphopantothenoylcysteine synthetase |
| PPCDC | = | (R)-4'-phospho-N-pantothenoylcysteine decarboxylase |
| PPAT | = | 4'-phosphopantetheine adenyltransferase |
| DPCK | = | Dephospho-CoA kinase |
| PD | = | Parkinson Disease |

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