

Pathological accumulation of iron in basal ganglia or other areas of brain has been known to be associated with a progressive disorder of nervous system since 1920's. Hallervorden-Spatz disease was in common usage for several decades. Due to advances in science that have unmasked several underlying genetic mutations in patients with brain iron accumulation² and also because of the links of Julius Hallervorden and Hugo Spatz to Nazi Germany in 1920s this has been replaced by NBIA (Neurodegeneration with brain iron accumulation)^{2,3,4}. NBIA are a heterogeneous group of genetically determined disorders that are characterized by iron deposition in several brain areas including basal ganglia manifesting with a progressive, extra pyramidal symptoms¹ (dystonia, parkinsonism, chorea), sometimes with pyramidal signs, cognitive dysfunction or ocular abnormalities.

NBIAs demonstrate wide heterogeneity in the phenotype, not only between subtypes but also amongst a given subtype. NBIAs are "ultra-rare" with a prevalence of <1/1000000 affected¹ but remain a differential diagnoses in both pediatric and adult onset neurodegenerative diseases and most neurologists or pediatric consultants will possibly encounter a handful of cases in their lifetime. It can be a difficult condition to diagnose and this article reviews current understanding of NBIAs to help clinicians with diagnosis and management of NBIAs.

How to diagnose

The diagnosis of NBIA requires-

- Identification of the phenotypes that are associated with NBIA
- MRI brain (with iron detecting sequences T2*/SWI/GRE) demonstrating deposition of iron in basal ganglia with or without white matter changes on T2 weighted imaging.
- Genetic testing for identification of specific subtype of the disease.

Genetic basis of NBIA

Several clearly defined genetic defects and some yet unidentified mutations can lead to NBIA.

Historically PANK 2 was first to be identified³ but over the last 2 decades, several conditions have been identified that manifest with NBIA. Aceruloplasminemia (described in 1987, gene identified in 2000) and neuroferritinopathy (identified in 2001), since 2004 have been included in NBIA⁵.

With the discovery of causative mutations in phospholipase A2 gene, Seitelberger disease also called infantile neuroaxonal dystrophy, was later renamed as PLA2G6 associated neurodegeneration.⁶

In 2008 the causative pathogenic mutation for Woodhouse Sakati syndrome was identified as c2orf37 mutation (also called as DCAF17 mutation).⁷ The invention of high field MRI in 1980s and later addition of sequences that could identify iron deposition in basal ganglia has helped clinicians to expand the spectrum of NBIA disorders⁸. The common genetic causes of NBIA are summarized in

TABLE 1- NBIA- GENES AND INHERITANCE TABLE 2 PATHOLOGICAL FEATURES OF NBIA

It can be debated if accumulation of iron in the brain is the primary process responsible for the degenerative changes, or secondary to neurodegeneration. Iron deposition in brain is known to be part of normal ageing and also commonly seen in MRI scans in other neurodegenerative disorders like Parkinson's disease, Multiple sclerosis, Multisystem atrophy etc.,

Contemporary understanding favors that the following factors play an important role in causing cell loss and iron accumulation⁹

- Mitochondrial dysfunction- mitochondria are the iron sink in cells and iron recycling in them is via mitophagy and lysosomal degradation of iron containing proteins. Altered mitochondrial fitness may hence affect iron turnover.
- Cell degeneration mediated through reactive oxygen species (specifically PANK2, PLA2G6)
- Altered lipid metabolism (PANK2, COASY, PLA2G6, FA2H, c19orf12)
- Altered mitophagy and autophagy (WDR 45, ATP13A2)

Differences in the relative contribution of each of the above processes can explain the heterogeneous pathological picture and possibly explain the varying phenotypes. The clinicopathologic variability is well known in NBIA. The ten subtypes can be further regrouped as⁹-

- **NBIA CAUSED BY DEFECTS IN GENES CODING FOR PROTEINS INVOLVED IN LIPID METABOLISM AND MEMBRANE HOMEOSTASIS** – PKAN, PLAN, FAHN, MPAN, CoPAN
- **NBIA CAUSED BY DEFECTS IN GENES CODING FOR PROTEINS OF IRON METABOLISM** – Aceruloplasminemia, Neuroferritinopathy
- **OTHER FORMS OF NBIA** – BPAN, Kufor Rakeb syndrome, WoodhouseSakati syndrome.

TABLE 3- PATHOGENESIS OF NBIAS

PHENOTYPE GENOTYPE CORRELATION OF NBIA-

Pantothenate kinase associated neurodegeneration (PKAN) -NBIA 1

PKAN is one of the commonest forms of NBIA encountered in clinical practice. PKAN can have heterogeneous phenotypes and it is useful to be classify this into classic and atypical variants¹².

Classic form has onset in first decade with gait or postural difficulty secondary to dystonia as the presenting symptom. Earlier in the course focal (cranial or limb musculature) dystonia is common. Axial dystonia predominates as disease advances. Oromandibular dystonia is common. A finding of jaw opening dystonia can be associated with a characteristic geste' antagoniste' that resembles a praying mantis. This geste with the patient touching the chin with both hands characteristically clenched into a fist with flexion at the elbows has been called "mantis sign' can be pathognomic of PKAN¹³. Dystonic opisthotonus or back arching has also been described as a characteristic feature of NBIAs related to PANK2 and PLA2G6 mutations.¹⁴ There can be mild developmental delay and corticospinal tract involvement. Retinitis pigmentosa and oculomotor abnormalities suggestive of midbrain degeneration like square wave jerks and poor convergence may be present¹². Seizures,

chorea, parkinsonism are rare¹⁵. Recurrent episodes of status dystonicus though rare are described in the classic variant^{12,15} The patient usually loses ambulation within 10-15 years in the classic form.

Atypical form is characterized by onset in second or third decade of life (rarely in seventh and eighth decades)¹⁶ The atypical disease has less severe dystonia and rigidity with slower progression to parkinsonism as compared to classic presentation.

Within atypical variant four predominant movement disorder phenotypes have been described.

The **dystonic phenotype** has early focal limb dystonia, dystonic tremor¹⁷, action induced dystonia, oromandibular dystonia with progression to generalized dystonia. Varying degrees of spasticity is seen. Although rare, PKAN can be seen in late onset focal dystonia and a patient with isolated blepharospasm at age of 55 has been described with PKAN ¹⁶.

The **parkinsonism phenotype** should be easy to pick up in young patients who have bradykinesia, rigidity, rest tremor or gait impairment. Speech abnormalities of stuttering, palilalia, hyophonia, spasmodic dysphonia are common and these might be the sole presenting feature or part of the early disease in a teenager or young adult. The parkinsonism can be levodopa responsive^{12,17}.

The other phenotypes that have been reported include isolated drug responsive freezing of gait ¹⁸, a choreic phenotype with senile chorea like presentation ¹⁹, motor tics and vocal tics²⁰, altered sleep architecture²¹and HARP syndrome (hypobetalipoproteinemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration) ^{22,23}.

PLA2G6 associated neurodegeneration (PLAN)- NBIA 2

This syndrome has a continuum of three age distinct but overlapping phenotypes^{24,25,26} of classic infantile neuroaxonal dystrophy, atypical neuroaxonal dystrophy of childhood onset including Karak syndrome and PLA2G6 –related dystonia- parkinsonism (PARK 14) of adult onset.

Classic infantile neuroaxonal dystrophy (NBIA 2a) is characterized by dystrophic axons found on nerve biopsy. is a devastating syndrome of neurodevelopmental regression. It accounts for 85% of the PLAN cases²⁶. The onset of disease is between 6 months- 2 years of age, with axial hypotonia,

psychomotor retardation which progress to gait disturbances (due to ataxia or postural instability)²⁷. The axial hypotonia is unique to this variant of PLAN and is not seen in other variants. Strabismus, nystagmus and optic atrophy, progressive pyramidal dysfunction with bulbar involvement^{27,28} are seen as disease advances. Generalized seizures have been reported²⁹. Many patients die in the first decade.

Atypical neuroaxonal dystrophy (NBIA 2b) has a childhood onset between 1- 6yrs of age¹⁵. The presentation is with gait instability (ataxia or postural instability) with dyspraxia and speech regression with two thirds of patient showing optic atrophy. The disease progresses with spastic tetraparesis, nystagmus, seizures, dystonia, dysarthria, cognitive disturbances with neuropsychiatric features.

Karak syndrome described by Mubaidin et.al³⁰ in 2003 is similar to atypical childhood onset PLAN and is due to homozygous missense mutation in PLA2G6 in 2006³¹, so it is grouped under atypical NAD category in 2009.

Adult onset PLAN/PLA2G6 associated dystonia parkinsonism/ PARK 14 | This is an adolescent or adult onset condition with subacute levodopa dystonia (blepharospasm, foot dystonia as presenting symptom) parkinsonism (rigidity and bradykinesia seen in majority), cognitive decline, oculomotor abnormalities, psychiatric features and pyramidal signs³². Cerebellar symptoms and signs are generally absent. Autonomic dysfunction (bladder or bowel disturbances) if present can be an important clue to the diagnosis of PLAN as this is not a feature of other NBIA subtypes. Neuropsychiatric features can be a presenting feature. The oculomotor disturbances like supranuclear gaze palsy, slow saccades, fragmented saccades, nystagmus, apraxia of eyelid opening can be seen³³. The parkinsonism is levodopa responsive and patients can develop levodopa induced dyskinesia^{27,34,35}.

Neuroferritinopathy- NBIA 3

This is the only autosomal dominantly inherited subtype of NBIA caused by mutation in ferritin light chain³⁶. Unlike other common NBIAs, the onset of neuroferritinopathy is in midlife³⁷. The phenotype is of slowly progressive movement disorder with subtle cognitive deficits. The movement disorder has a focal onset chorea (39.7%), lower limb dystonia (38.5%), parkinsonism (6%) and tics (1.2%), tremor (7.2%), cerebellar ataxia (4.2%)³⁸. There is striking asymmetry throughout the disease³⁷. The triad of oromandibular dyskinesia (65%), impairment of voice and speech (dysarthrophonia) with action-specific facial dystonia (63%) is specific to neuroferritinopathy. Pyramidal dysfunction, oculomotor abnormalities (slow saccades, apraxia of eyelid opening, limitation of vertical eye movements), sleep disturbances, vibration and proprioception loss can develop later. Frontal executive dysfunction may develop early³⁹ or late. A case of adult onset isolated cranio cervical dystonia with later development of parkinsonism identified as NFT has also been described¹⁶.

Mitochondrial membrane-protein associated neurodegeneration (MPAN) NBIA- 4

This is an autosomal recessive NBIA described by Hartig et.al in 2011 caused by mutations in c19orf12 gene⁴⁰. The mean age of onset is 11 years⁴¹. The condition is characterized by progressive spastic paraplegia, parkinsonism unresponsive to L-DOPA treatment, psychiatric or behavioral symptoms, with variable optic atrophy and motor axonal neuropathy. The onset of disease is similar to that seen in PKAN and PLAN with gait or speech abnormalities, focal dystonia restricted to feet and hands, oromandibular dystonia, with early pyramidal dysfunction (lower limbs more affected than upper limbs).

Motor axonal neuropathy has been observed in 39% to 44% of the patients^{40,41}. In advanced disease, progressive muscle atrophy makes the differentiation from atypical PKAN and PLAN easier. Optic atrophy has been reported in 74% of patients⁴¹. Cognitive decline is very common with inattention, hyperactivity, emotional lability, and depression, as well as stereotypic hand movements.

Beta-propeller protein-associated neurodegeneration (BPAN) NBIA 5

This X linked dominant disease previously called as SENDA^{21,22} has been renamed as BPAN after the causative gene mutation in WDR45 gene was identified in 2012⁴².

There are two phases of disease progression in SENDA. In childhood, there is generally delayed speech and motor development with ataxic gait with preserved gait stability till adolescence/adulthood⁴³, usually in late adolescence early adulthood, there is a deterioration of neurological status with rapid development of parkinsonism, dystonia and cognitive decline. Seizures can be seen in childhood but are rare later in the course. The parkinsonism is levodopa responsive with early development of motor fluctuations and disabling dyskinesias. The dystonia starts in upper limbs with possible development of camptocormia. There is rapid progression of disease with spastic paraparesis and dysphagia. Hypersomnolence with shortened sleep onset latency on MSLT and abnormal REM sleep can be seen. A characteristic dance like movement of extremities with onset of sleep has been noted. A Rett's syndrome like phenotype with repetitive midline hand wringing movements has been reported⁴³ and is one of the important differentials for atypical Rett's phenotype. In advanced stages patients are bed bound and profoundly demented. Colobomata, astigmatism, myopia, loss of pupillary ruff are the ocular abnormalities reported.

COASY protein associated neurodegeneration (COPAN)- NBIA 6

A homozygous mutation of COASY which encodes for Coenzyme A synthase is causes this condition⁴⁴. The cases reported in literature had normal development till the age of two

years but later developed gait abnormality progressed to spastic quadriparesis with dystonia parkinsonism. Oromandibular dystonia, cognitive decline and mild axonal neuropathy have been described in the patients with this NBIA.

Aceruloplasminemia-

Aceruloplasminemia is caused by mutation in ceruloplasmin gene⁴⁵ with an average age at diagnosis is 51 years. A clinical triad of retinal degeneration, diabetes mellitus and neurologic symptoms/signs and anemia predates the development of diabetes and neurological symptoms. In a recent review⁴⁶ the most common presenting symptom was cerebellar dysfunction in 71%, hyperkinetic movement disorder in 64% (dystonia-blepharospasm and oromandibular dystonia, tremor, chorea), parkinsonism in 20%, and cognitive dysfunction in 60% (apathy and memory impairment).

Fatty acid 2 hydroxylase associated neurodegeneration (FAHN)

The mutation in the gene encoding for fatty acid 2 hydroxylase was identified in 2010⁴⁷. The phenotype is similar to that of infantile PLAN and many other leukodystrophies with onset in the first decade of gait impairment and falls progressing to spastic quadriparesis, dystonia, cerebellar dysfunction, variable optic atrophy, divergent strabismus, seizures. Most of the patients became wheel chair bound by adolescence⁴⁷. Axonal neuropathy was reported in a single family⁴⁸.

Kufor Rakeb syndrome-

This NBIA disorder was described in 1994 from Jordan⁴⁹. The chromosome 1p locus was designated as PARK9 locus for the monogenic parkinsonian phenotype. The causative

compound heterozygous gene mutation was identified in 2006 in lysosomal ATP13A2. It is a syndrome of juvenile onset parkinsonism, spasticity, supranuclear gaze palsy²⁵ and cognitive features (visual hallucinations and dementia). Oculogyric dystonic spasms, facial-facial-finger mini-myoclonus and autonomic dysfunction are variably associated.

The parkinsonism is initially responsive to levodopa with early development of disabling dyskinesias and hallucinations. Dystonia develops in 50% of the cases later in the disease course⁴⁹.

Cerebellar features are rare but there is marked olfactory dysfunction. In the first ever case of Kufor Rakeb syndrome reported from India recently, a novel nonsense mutation in ATP13A2, and clinically he had no cognitive dysfunction, myoclonus or hallucinations and a slow clinical progression⁵⁰

Woodhouse Sakati syndrome-

This is a rare neuroendocrine disorder described in 1983. The causative gene mutation has been identified in c2orf37 gene in 2008.⁷The clinical presentation is dysmorphic facies (alopecia, high forehead, malocclusion), hypogonadism, diabetes mellitus, mental retardation, sensorineural deafness and extrapyramidal features. Seizures, polyneuropathy, thyroid dysfunction, keratoconus and syndactyly of hand or feet have been described in some of the cases. Thrombocytopenia has been reported in a family of three affected siblings from India⁵¹.The extrapyramidal features and diabetes may not develop till late teens or early adulthood. The movement disorder phenotype is reported only in 50% cases as a combination of focal onset chorea and dystonia with progression and later gait difficulty and immobilization. Eye movements are normal. Deafness and cognitive decline or mental retardation is seen in 75% of patients. This syndrome forms an important differential diagnosis for deafness- dystonia phenotype from Mohr-Tranejberg disease.

Leukoencephalopathy with dystonia and motor neuropathy – SCP2 MUTATIONS

A NEW NBIA PHENOTYPE?

There are two case reports of this condition in the literature to date. The causative mutation was identified to be in the gene encoding sterol carrier protein leading to its deficiency. It was first described in 2006 in a 45 yr old male with 28 yr history of spasmodic torticollis, spinocerebellar ataxia and motor neuropathy⁵². MRI brain showed no iron deposition of basal ganglia but a leukoencephalopathy and hyperintense thalamus and pons (butterfly like lesions) but with no iron deposition. In 2015 the second case was reported of a 55 year old male with twenty year history of spinocerebellar ataxia, gait disturbance and deafness with no extrapyramidal disturbances⁵³ but MRI brain demonstrated iron deposition and no leukoencephalopathy.

GTPBP2 mutations and NBIA

A family of three siblings⁵⁴ have been described with this mutation presenting with delayed developmental milestones and later developed action dystonia of hands and feet, ataxia motor neuronopathy and cognitive decline (low IQ and neuropsychiatric disturbances). The MRI brain of all the three sibs demonstrated hypointense globus pallidi and substantia nigra on T2* imaging with cerebellar vermian atrophy. The causative mutation was in the GTPBP gene encoding for GTP binding protein 2 (GTP superfamily are enzymes involved in cell proliferation and differentiation, intracellular transport)

Radiological features of NBIA-

MRI brain (T1, T2, T2* and FSE) sequences are very useful for the diagnosis and to differentiate between various NBIA syndromes⁵⁵.

Within the brain parenchyma there are certain areas which are inherently rich in iron- globus pallidus, substantia nigra, red nucleus, dentate nucleus, putamen and thalamus. With normal aging there is an increased iron deposition within basal ganglia and dentate nuclei. In NBIA s there is symmetric distribution of excess iron accumulation in the iron rich areas of brain mentioned above. Iron appears isointense on T1 weighted and hypointense on T2 weighted imaging. Calcium also appears isointense on T1 and hypointense on T2 but CT scan differentiates the two as calcium is hyperintense than surrounding brain parenchyma on CT and iron is isointense.

The MRI workup of NBIA is incomplete without T2* weighted acquisitions and /or SWI imaging. They enhance this degree of hypointensity(described as “blooming”).All NBIA subtypes reveal iron deposition in globuspallidi on MR imaging but differ in the co-occurrence of other findings⁵⁶.

TABLE 4- IMAGING FEATURES IN NBIA

Approach to a patient with suspected NBIA-

Usually in a pediatric or neurology/ movement disorders clinic a clinician encounters a patient with a mixed bag of neurological symptoms/ signs and an abnormal MRI brain showing iron deposition. Sometimes the report from a radiologist can state NBIA with classic features like “eye of a tiger sign” that can ease the diagnostic burden. More commonly, we as clinicians will have to unjumble the puzzle with a re-visit and look for more clinical clues that facilitate diagnosis. Genetic diagnosis is not always possible as most of the mutations have been described in a small group of patients. A detailed clinical history and examination can be very helpful. It is not always easy to get the correct age of onset, course and Progression. One should look for associated features like retinitis pigmentosa, optic atrophy, peripheral neuropathy, seizures, cognitive decline/neuropsychiatric features, cerebellar features, endocrine abnormalities.

Then the next step is to investigate towards the specific subtype with laboratory, electrophysiological and MR imaging of brain with the iron specific sequences.

Laboratory investigations include hemogram for anemia, serum and urine copper levels, serum ceruloplasmin, serum ferritin, iron levels, blood sugar, hormone level testing for hypogonadism where appropriate. Neuroferritinopathy has low serum ferritin levels with all other parameters being normal whereas aceruloplasminemia has low or absent serum ceruloplasmin, elevated ferritin, low iron, and low serum copper but normal urinary copper and raised blood sugar levels. Serum hormonal assays are to be done in suspected cases of Woodhouse Sakati syndrome.

EEG can be helpful if seizures are in question as in PLAN- INAD and atypical NAD (but not in PLAN-DP), FAHN, BPAN, and Woodhouse Sakati syndrome.

EMG studies should be done to look for sensorimotor neuropathy in case neuropathy is suspected as in PLAN, motor neuronopathy/axonopathy in MPAN.

Sleep analysis can be helpful to investigate and manage reduced sleep time insomnia and sleep apnea. Abnormal REM sleep with decreased sleep onset latency and hypersomnolence can be seen in BPAN and may require Polysomnography and MSLT to look for this.

The MRI is usually available by the time the one starts thinking of NBIA but a detailed MRI with iron specific sequences and T2 W images can help narrow down the diagnosis.

Genetic testing can confirm the diagnosis but not all NBIA cases will have either of the mutations described and there are still some unknown NBIA's. The advancement of genetic diagnosis and whole genome sequencing has meant that sometimes one may see a patient

in clinic for the first time who comes with a genetic diagnosis. This is not easy to interpret genetic results in an asymptomatic patient or in someone with minimal signs. It is important to understand that not all mutations in the known genes causing NBIA are pathogenic, so one must be careful in interpreting genetic results. OMIM usually lists commonly known mutations but one might want to seek help from an expert neurogeneticist who have a better understanding of these mutations and have access to larger genetic databases to confirm in case of a doubt about pathogenicity of a newly found mutation with minimal or no clinical signs. MRI can help as well to look for changes in asymptomatic patients with these mutations.

Management

Although there are some trials currently underway for specific treatments, the management of NBIA to date remains symptomatic. A multidisciplinary approach to therapy is recommended with a combination of medical, surgical and good supportive/nursing care/physiotherapy. The medical therapy for dystonia with trihexiphenidyl, and spasticity with benzodiazepines, baclofen can be tried but the response is variable and not sustained¹⁵. Botulinum toxin therapy is particularly useful for drug resistant dystonia especially oromandibular dystonia and salivary gland toxin injections for drooling in advanced cases. In patients with NBIA and parkinsonism, levodopa trial is always justified. Parkinsonism in PKAN is not levodopa responsive, where as in PLAN (childhood onset and dystonia parkinsonism), MPAN, BPAN and Kufor Rakeb syndrome respond initially but the early development of disabling dyskinesias and hallucinations can be seen. Dopamine agonists should be used very cautiously in NBIA specially with neuropsychiatric or cognitive problems as evidence of success is limited.

A preliminary study of deferiprone, an oral iron chelator showed robust reduction of brain iron on brain MRI in PKAN patients, but no measurable benefit in clinical disease outcomes⁸⁸.

Intrathecal baclofen pump can be used for symptomatic management of dystonia/spasticity where oral medications have failed or not advisable in view of dysphagia. Of recent interest is a novel intraventricular baclofen delivery in nine children which included one PKAN patient⁸⁹, but additional studies are required.

Deep brain stimulation has been offered to very few patients with NBIA and there is insufficient data in literature to guide usage of DBS. This can be reviewed with local teams with expertise in DBS management of dystonia and Parkinson's on a case to case basis. In a PKAN patient some improvement was noted after bilateral GPi DBS (improvement in BFDQRS scale) it was not persistent and the benefit diminished with time²⁵. The dystonic storm of classical PKAN patients is resistant to drugs and GPi DBS has been reported to be life saving⁹⁰.

Good supportive care with a multidisciplinary team including physiotherapy, occupational therapy, psychology support, speech and language therapy and nursing care remains the mainstay of management of patients with NBIA.