

Dystonia and Brain Iron Accumulation

An Overview of the Current Understanding, Diagnosis and Treatment of Neurodegeneration with Brain Iron Accumulation

Introduction

The term 'dystonia' describes "the disordered tonicity of muscle tissue"(1). In clinical practice 'dystonia' describes a vast spectrum of conditions involving uncontrollable and sometimes painful muscle spasm, with varying degrees of impact on a patient's quality of life. In most cases the aetiology of dystonia is unknown; the accumulation of brain iron is a rare but well-recognised cause of a heterogeneous group of neurodegenerative conditions, including dystonia (2).

Hallervorden and Spatz first described a progressive neurological condition with accumulation of iron in the basal ganglia in the 1920s (3). The later development of MRI allowed non-invasive imaging of iron in the brain, and so since the 1980s our understanding of this disease has vastly improved (4). There are now a number of recognised forms of neurodegeneration with brain iron accumulation (NBIA) and several causative genes have been identified.

Although the symptoms of NBIA are many and various, including cognitive impairment, behavioural change, oculomotor disturbance, chorea and parkinsonism, the most prominent feature is invariably dystonia (2). This is certainly true of the only patient I have met with NBIA: a nine year-old boy I met while on a paediatric placement, who had developed normally until the age of three and a half years, when his family noticed that he was becoming unsteady on his feet. Over the next few months he stopped walking altogether and NBIA was diagnosed following an MRI scan of his brain several months after that. This young boy's father told me with startling frankness how, despite medicine's best efforts, the relentless progression of his son's dystonia has had a devastating impact on his family's lives.

In the following pages I will discuss the current understanding of the pathophysiology and aetiology of NBIA, the common clinical presentations of the most common subtypes, the methods of diagnosis and the types of treatment currently available.

Pathophysiology and Aetiology

Iron is a vital component for the normal functioning of the brain, specifically the synthesis of neurotransmitters and DNA and the production of energy (5). Even in a healthy brain iron is not evenly distributed, with higher levels of iron found in specific areas such as the globus pallidus, substantia nigra and dentate nucleus (6). In NBIA a higher than usual concentration of iron is seen in the basal ganglia, specifically in the globus pallidus and substantia nigra (7). The accumulation of iron in the basal ganglia is not only seen in NBIA but also in other movement disorders such as Parkinson's disease and Huntingdon's disease (8).

The mechanism by which iron accumulates in the basal ganglia is poorly understood, but it is recognised that ferrous iron reacts with endogenous hydrogen peroxide to form reactive oxygen species. In areas of the brain with a large accumulation of iron, the degree of oxidative stress caused by these reactive oxygen species is sufficient to result in neuronal death (9).

Several distinct subtypes of NBIA have now been described, which differ in both their clinical presentation and their genetic aetiology. The two most common subtypes (pantothenate kinase-associated neurodegeneration and PLA2G6-associated neurodegeneration, also known as NBIA1 and NBIA2, respectively) will be discussed in detail below. Intriguingly, none of the causative genes so far identified in association with either of the most common subtypes of NBIA is directly involved in the metabolism of iron in the brain (10), raising the interesting question of whether it is iron accumulation causing neuronal damage, or whether iron accumulation is actually the result of another neurodegenerative disease process.

Approximately half of all cases of NBIA are pantothenate kinase-associated neurodegeneration (PKAN), caused by mutations in the PANK2 gene on chromosome 20p (11). The PANK2 gene is one of several genes which encode a class of protein called pantothenate kinase, which catalyses the phosphorylation of vitamin B5 (pantothenate), in the first step in the production of coenzyme A. PANK2 is unique amongst the genes encoding for these proteins because it is the only one which is exclusively expressed in the mitochondria of neurons in the human brain (12). Coenzyme A (CoA) is a vital cofactor in many biological processes (13), however it is still not understood how a reduction in CoA levels causes iron to accumulate in cells, and, given that PANK2 is expressed in mitochondria of cells throughout the brain, why iron accumulation in PKAN should be limited to the basal ganglia and particularly to the globus pallidus (14).

The accumulation of iron in the globus pallidus is not the only histological abnormality observed in PKAN. Axonal spheroids (swellings) are also found in the globus pallidus of patients with PKAN at post-mortem. The nature of these spheroids has been the subject of much study which has been complicated by the fact that NBIA, once thought to be a single disease with a wide spectrum of presentations, has been shown to be in fact a group of discrete disorders, each with a different aetiology, but all involving iron accumulation in the basal ganglia. The spheroids seen in PKAN are evidence of neuronal degeneration, which have recently been shown to contain high concentrations of an as-yet unidentified abnormal protein (15).

Axonal spheroids are also an important histopathologic feature of PLA2G6-associated neurodegeneration (PLAN), the second most common form of NBIA. PLA2G6 encodes for the iPLA₂ enzyme, a phospholipase which is involved in fatty acid metabolism. This process is vital to the integrity of the axonal cell membrane and it is possible that the resulting instability of the membrane is responsible for the formation of these spheroids. The composition of spheroids in PLAN differs from those in PKAN and is better defined; it has been shown that spheroids in patients with

confirmed PLAN contain Lewy bodies (made up of a protein called α -synuclein) and threads of phosphorylated tau protein (16).

Two subtypes of NBIA have been described which differ in aetiology from PKAN and PLAN: neuroferritinopathy and aceruloplasminaemia. In both these conditions the causative mutations are found in genes which encode for proteins known to have a direct role in the metabolism of iron (unlike PKAN and PLAN, in neither of which is the genetic mutation directly implicated in the iron metabolism pathway) and like PKAN and PLAN they cause a disabling dystonia.

Neuroferritinopathy is the only autosomal-dominant form of NBIA and is very rare, having been described in only a small number of families (17). Families with neuroferritinopathy carry a mutation in the ferritin light gene, which encodes the ferritin light polypeptide, a subunit of the ferritin complex which is responsible for storage and detoxification of iron within cells (18).

Aceruloplasminaemia is an autosomal-recessive disorder characterised by the truncation of the ceruloplasmin enzyme. This enzyme is vital for normal iron homeostasis as it oxidises Fe^{2+} to Fe^{3+} in a controlled manner without the formation of the dangerous free radicals produced in non-enzymatic oxidation of iron (19). In the normal central nervous system the gene for ceruloplasmin is expressed by astrocytes, where the ceruloplasmin works in cooperation with a membrane iron transporter to oxidise and remove iron from the astrocytes. In patients with aceruloplasminaemia, in whom there is no functioning ceruloplasmin to effect this removal of iron, iron accumulates in the astrocytes. This accumulation in the brain is specific to the basal ganglia, although as with the other forms of NBIA, it is not understood why this particular region of the brain should be so selectively affected (19).

Clinical presentation

PKAN was formerly known as Hallervorden-Spatz disease (re-named in light of the involvement of both Hallervorden and Spatz in the Nazi regime), and its typical presentation is in the first few years

of life (usually before 6 years) with difficulties with gait and posture (20). Atypical presentations of PKAN are usually later (typically during teenage years, but onset may be as late as early adulthood) and the phenotype in these cases may also be atypical; cognitive features may become apparent before the development of any movement disorder (21). The typical, or so-called 'classic', form of PKAN shows great clinical homogeneity, following a predictable and rapid symptomatic progression over the course of a few years. In contrast atypical PKAN appears to have a much wider spectrum of severity; cases have been reported of patients with PKAN (confirmed with molecular genetic testing) whose onset of symptoms was not until their 20s and who are living with only minimal symptoms decades later (17).

PLAN is the second most common NBIA syndrome, and like PKAN, the disease seems to show two distinct age distributions. The early onset form of the disease presents with infantile neuroaxonal dystrophy, a relentlessly progressive combination of dystonia and cognitive regression, while later-onset cases tend to be a more slowly progressive dystonia with prominent parkinsonian features and often represent a less severe end of the spectrum of the disease (22, 23).

Both neuroferritinopathy and aceruloplasminaemia present in adulthood (17). Neuroferritinopathy has an onset much like that of Huntington's disease, with prominent cognitive changes and initial choreiform movements with the gradual development of dystonia (24). Aceruloplasminaemia is unique amongst the spectrum of NBIA diseases because it causes iron to accumulate not only in the brain but also in other organs of the body, such as the liver, the pancreas and the retinae (25). This widespread deposition of iron is reflected in the wide range of presenting symptoms, including not only neurodegeneration (typically dystonia including blepharospasm and dementia) but also visual impairment and diabetes mellitus, due to involvement of the retinae and pancreas respectively (26).

Diagnosis and imaging of NBIA

Developments in high field MRI have revolutionised the diagnosis of NBIA; prior to this a definitive diagnosis was only possible at autopsy, when histochemical staining could show the presence of increased levels of iron in the basal ganglia. PKAN specifically is associated with the characteristic 'eye of the tiger' sign surrounding the globus pallidus, with a central hyperintense area surrounded by a region of hypointensity, which is seen on T2-weighted images (27). T2-weighted imaging of patients with PLAN also shows an area of hypointensity around the globus pallidus, but without the central hyperintensity which characterises PKAN (28).

The 'eye of the tiger' sign on T2-weighted images is almost exclusively diagnostic of PKAN, however work by McNeill and colleagues has shown that it can also be seen in some patients with neuroferritinopathy, in whom changes in the caudate and putamen may also be seen, allowing neuroferritinopathy to be accurately distinguished from other types of NBIA (29).

Although extremely useful in distinguishing between subtypes of NBIA, MRI is mostly used in practice to guide clinicians as to the most appropriate molecular genetic testing for the patient (11).

Transcranial sonography (TCS) has been used in the diagnosis of movement disorders for several years, specifically in cases of suspected Parkinson's disease, where it can show the degeneration of the substantia nigra (30). Because the substantia nigra is one of the regions of the brain in which iron accumulates in NBIA, it has been hypothesised that TCS could be of use in diagnosing NBIA. Although TCS gives far less diagnostic information than MRI and is unable to distinguish between different subtypes of NBIA, the advantage of its use is clear: the majority of patients undergoing investigation for NBIA are young children with severe movement disorder and therefore in order to undergo MRI they must be anaesthetised to prevent movement artefacts on the images. TCS has recently been shown to be a quick and safe method which is able to identify patients with iron accumulation in the substantia nigra, and it therefore has the potential for use as an early screening method in patients where NBIA is suspected (31).

Despite advances in imaging which allow the identification of iron accumulation and the delineation of different subtypes of NBIA, currently the only definitive diagnosis for any of the subtypes described above (PKAN, PLAN, neuroferritinopathy and aceruloplasminaemia) is through genetic testing and the identification of the causative genetic mutation. Those patients in whom none of the known mutations can be found are labelled with the rather unsatisfactory term 'idiopathic NBIA', making it clear that there are many mutations causing NBIA which are yet to be identified.

Therapy: now and in the future

The understanding of the spectrum of NBIA and its aetiology is in its infancy, and as such the treatments that are currently in use for patients suffering from NBIA are targeted towards symptomatic relief and not at the underlying cause. For the dystonia and spasticity, which are the most disabling symptoms, baclofen and trihexyphenidyl are the most effective drug therapies. Baclofen is particularly useful in these patients, as when they are no longer able to tolerate oral treatment it can be given intrathecally through a pump. For patients suffering from severe parkinsonian symptoms (such as patients with the late-onset form of PLAN) levodopa may also prove useful (11).

Deep brain stimulation (DBS) has been used for many years in the treatment of Parkinson's disease and DBS of the internal globus pallidus has recently been integrated into the management of patients with NBIA for the relief of dystonic symptoms. Trials show an initial improvement in patients, but sadly this remission seems to be only short-lived and does not prevent the progression of the dystonia (32).

It seems logical that if excess iron is the cause of symptoms in NBIA then iron chelation therapy would be the obvious cure. Deferiprone is an iron chelating agent which is administered orally and capable of crossing the blood-brain barrier, making it the agent of choice for chelating brain iron. There has been some success in using deferiprone therapy in Friedreich's ataxia, a related

movement disorder in which there is also deposition of iron in the brain (33). Although Kwiatkowski and colleagues have had some success in improving the dystonic symptoms of a patient with NBIA in a single case study, iron chelation is yet to be thoroughly researched to see whether it is truly of benefit to patients with NBIA (34).

PKAN was the first of the NBIA subtypes to be described and is currently the subtype about which we understand the most. An understanding of the mechanism by which PKAN causes symptoms reveals another potential therapeutic target in addition to iron chelation. Rana and colleagues have used a drosophila model for PKAN to study its aetiological mechanism and to test possible treatments for the disease. As discussed above, pantothenate kinase is an enzyme vital to the production of coenzyme A and which is inactive in patients with PKAN due to a hereditary genetic mutation. The PKAN drosophila models (with no functional pantothenate kinase) had markedly reduced levels of CoA, but feeding the drosophila with pantethine (an active form of vitamin B5) was effective in restoring the CoA levels to normal and improving the mobility of the drosophila (35). Although it is still only in the early stages of research, the use of pantethine in practice is an exciting prospect in the treatment of NBIA.

Conclusion

NBIA is a cause of dystonia which we are only beginning to understand; extensive research into both the causative genetic mutations and the underlying mechanisms of this group of disorders is providing us with hope for a future cure for these debilitating conditions.

Since the first description of NBIA in the 1920s advances in imaging technology and genetic testing mean that we can now accurately diagnose patients during their lifetimes, instead of waiting for post-mortem histology. This creates a window of opportunity for treating not only the patient's symptoms, but also potentially the underlying cause of their disease. Current treatment is symptomatic, with a combination of muscle-relaxant drugs and DBS in those patients for whom it is

appropriate. Future treatments will use our improved understanding of the mechanisms of these diseases as therapeutic targets: for example, oral iron chelation therapy in all NBIA subtypes and pantethine specifically in PKAN.

For many years the future has seemed bleak for sufferers of NBIA and their families. The volume of research currently in progress and the rate at which our understanding of these diseases changes and improves should make us hopeful that more effective treatments and potential cures are within our reach.

References

1. OED. Oxford English Dictionary.
<http://www.oed.com/view/Entry/242655?redirectedFrom=dystonia#eid> 2012.
2. Schneider SA, Hardy J, Bhatia KP. Syndromes of neurodegeneration with brain iron accumulation (NBIA): An update on clinical presentations, histological and genetic underpinnings, and treatment considerations. *Movement Disorders*. 2012;27(1):42-53.
3. Hallervorden J, Spatz H. Eigenartige erkrankung im extrapyramidalen system mit besonderer beteiligung des globus pallidus und der substantia nigra - Ein beitrag zu den beziehungen zwischen diesen beiden zentren. *Zeitschrift für die gesamte Neurologie und Psychiatrie*. 1922;79(1):254-302.
4. Stankiewicz J, Panter SS, Neema M, Arora A, Batt CE, Bakshi R. Iron in Chronic Brain Disorders: Imaging and Neurotherapeutic Implications. *Neurotherapeutics*. 2007;4(3):371-86.
5. Crichton RR, Dexter DT, Ward RJ. Brain iron metabolism and its perturbation in neurological diseases. *Journal of Neural Transmission*. 2010:1-14.
6. Thomas M, Jankovic J. Neurodegenerative disease and iron storage in the brain. *Current Opinion in Neurology*. 2004;17(4):437-42.
7. Gregory A, Hayflick SJ. Neurodegeneration with brain iron accumulation. *Folia Neuropathologica*. 2005;43(4):286-96.
8. Dusek P, Jankovic J, Le W. Iron dysregulation in movement disorders *Neurobiology of Disease*. 2012;46(1):1-18.

9. Rouault T, Cooperman S. Brain Iron metabolism. *Seminars in Pediatric Neurology*. 2006;13:142-8.
10. Keogh MJ, Chinnery PF. Current Concepts and Controversies in Neurodegeneration with Brain Iron Accumulation. *Seminars in Pediatric Neurology*. 2012;19(2):51-6.
11. Gregory A, Polster BJ, Hayflick SJ. Clinical and genetic delineation of neurodegeneration with brain iron accumulation. *Journal of Medical Genetics*. 2009;46(2):73-80.
12. Kotzbauer P, Truax A, Trojanowski J, Lee V. Altered neuronal mitochondrial coenzyme A synthesis in neurodegeneration with brain iron accumulation caused by abnormal processing, stability, and catalytic activity of mutant pantothenate kinase 2. *Journal of Neuroscience*. 2005;25(3):689-98.
13. Leonardi R, Zhang YM, Rock CO, Jackowski S. Coenzyme A: Back in action. *Progress in Lipid Research*. 2005;44(2-3):125-53.
14. Prohaska R, Sibon OCM, Rudnicki DD, Danek A, Hayflick SJ, Verhaag EM, et al. Brain, blood, and iron: Perspectives on the roles of erythrocytes and iron in neurodegeneration. *Neurobiology of Disease*. 2012;46(3):607-24.
15. Kruer MC, Hiken M, Gregory A, Malandrini A, Clark D, Hogarth P, et al. Novel histopathologic findings in molecularly-confirmed pantothenate kinase-associated neurodegeneration. *Brain*. 2011;134(4):947-58.
16. Paisán-Ruiz C, Li A, Schneider SA, Holton JL, Johnson R, Kidd D, et al. Widespread Lewy body and tau accumulation in childhood and adult onset dystonia-parkinsonism cases with PLA2G6 mutations. *Neurobiology of Aging*. 2012;33(4):814-23.

17. Gregory A, Hayflick SJ. Genetics of neurodegeneration with brain iron accumulation. *Current Neurology and Neuroscience Reports*. 2011;11(3):254-61.
18. Dusek P, Schneider SA. Neurodegeneration with brain iron accumulation. *Current Opinion in Neurology*. 2012;25(4):499-506.
19. Vassiliev V, Harris ZL, Zatta P. Ceruloplasmin in neurodegenerative diseases. *Brain Research Reviews*. 2005;49(3):633-40.
20. Hayflick S. Neurodegeneration with brain iron accumulation: from genes to pathogenesis. *Seminars in Pediatric Neurology*. 2006;13(1):182-5.
21. Aggarwal A, Schneider SA, Houlden H, Silverdale M, Paudel R, Paisan-Ruiz C, et al. Indian-subcontinent NBIA: Unusual phenotypes, novel PANK2 mutations, and undetermined genetic forms. *Movement Disorders*. 2010;25(10):1424-31.
22. Kurian MA, Morgan NV, MacPherson L, Foster K, Peake D, Gupta R, et al. Phenotypic spectrum of neurodegeneration associated with mutations in the PLA2G6 gene (PLAN). *Neurology*. 2008;70(18):1623-9.
23. Paisan-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. *Annals of Neurology*. 2009;65(1):19-23.
24. Wild EJM, Eise E ; Sweeney, Mary G ; Schneider, Susanne A ; Beck, Jon ; Bhatia, Kailash P ; Rossor, Martin N ; Davis, Mary B ; Tabrizi, Sarah J. Huntington's disease phenocopies are clinically and genetically heterogeneous. *Movement Disorders*. 2008;23(5):716-20.
25. Nittis T, Gitlin JD. The copper-iron connection: Hereditary aceruloplasminemia. *Seminars in Hematology*. 2002;39(4):282-9.

26. Miyajima H, Nishimura Y, Mizoguchi K, Sakamoto M, Shimizu T, Honda N. Familial apoceruloplasmin deficiency associated with blepharospasm and retinal degeneration. *Neurology*. 1987;37(5):761-7.
27. Kruer MC, Boddaert N, Schneider A, Houlden H, Bhatia KP, Gregory A, et al. Neuroimaging features of neurodegeneration with brain iron accumulation. *American Journal of Neuroradiology*. 2012;33(3):407-14.
28. Schneider SA, Bhatia KP. Syndromes of Neurodegeneration With Brain Iron Accumulation. *Seminars in Pediatric Neurology*. 2012;19(2):57-66.
29. McNeill A, Birchall D, Hayflick SJ, Gregory A, Schenk JF, Zimmerman EA, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. *Neurology*. 2008;70(18):1614-9.
30. Becker G, Seufert J, Bogdahn U, Reichmann H, Reiners K. Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography. *Neurology*. 1995;45(1):182-4.
31. Liman J, Wellmer A, Rostasy K, Bähr M, Kermer P. Transcranial ultrasound in neurodegeneration with brain iron accumulation (NBIA). *European Journal of Paediatric Neurology*. 2012;16(2):175-8.
32. Zorzi G, Zibordi F, Chiapparini L, Nardocci N. Therapeutic Advances in Neurodegeneration With Brain Iron Accumulation. *Seminars in Pediatric Neurology*. 2012;19(2):82-6.
33. Boddaert NLQS, KH ; Rotig, A ; Leroy-Willig, A. ; Gallet, S. ; Brunelle, F. ; Sidi, D. ; Thalabard, JC. ; Munnich, A. ; Cabantchik, ZI. Selective iron chelation in Friedreich ataxia. *Bloo*. 2007;110(1):401-8. Epub March 2007.

34. Kwiatkowski A, Ryckewaert G, Jissendi Tchofo P, Moreau C, Vuillaume I, Chinnery PF, et al. Long-term improvement under deferiprone in a case of neurodegeneration with brain iron accumulation. *Parkinsonism & Related Disorders*. 2012;18(1):110-2.
35. Rana A SE, Siudeja K, Muntendam R, Srinivasan B, van der Want JJ, Hayflick S, Reijngoud DJ, Kayser O, Sibon OC. Pantethine rescues a *Drosophila* model for pantothenate kinase-associated neurodegeneration. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(15):6988-93.