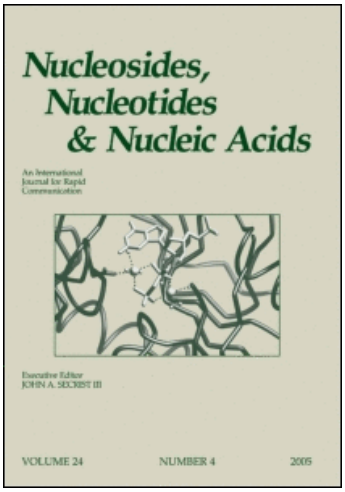

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Medical Diagnosis, Management and Treatment of Lesch Nyhan Disease

Gillian McCarthy[a]
[a] Chailey Heritage Clinical Services, North Chailey, East Sussex, UK

Online publication date: 27 October 2004

To cite this Article McCarthy, Gillian(2004) 'Medical Diagnosis, Management and Treatment of Lesch Nyhan Disease', Nucleosides, Nucleotides and Nucleic Acids, 23: 8, 1147 — 1152
To link to this Article: DOI: 10.1081/NCN-200027395
URL: http://dx.doi.org/10.1081/NCN-200027395

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 23, Nos. 8 & 9, pp. 1147–1152, 2004

Medical Diagnosis, Management and Treatment of Lesch Nyhan Disease

Gillian McCarthy, F.R.C.P., F.R.C.P.C.H.*

Chailey Heritage Clinical Services, North Chailey, East Sussex, UK

ABSTRACT

The aim of this presentation is to inform about Lesch Nyhan Disease from the point of view of the affected boys and their families living with the condition from day to day and also to show the importance of research in treating and managing the disease (In *Caring for Children with Lesch Nyhan Disease—A Guide for Parents and Professionals*; McCarthy, G.T., Ed.; PUMPA and Chailey Heritage Clinical Services: East Sussex, UK, 2002).

Key Words: Lesch Nyhan Disease; Diagnosis; Management; Treatment.

INTRODUCTION

Lesch Nyhan Disease (LND) is one of the so-called 'Orphan Diseases.' It is extremely rare. In a country the size of the United Kingdom, population 56 million, only 4 new cases will occur each year. It is one of 28 genetic metabolic disorders of purine metabolism and of the more than 1300 inherited disorders now recognised. It is X linked but rare female cases have been reported. It derives its name from the two astute clinicians in the USA who in 1964 recognised a recurring pattern of neurological abnormalities in 2 young boys from the same family.

*Correspondence: Gillian McCarthy, F.R.C.P., F.R.C.P.C.H., Chailey Heritage Clinical Services, North Chailey, East Sussex, BN8 4JN, UK.

DOI: 10.1081/NCN-200027395
1525-7770 (Print); 1532-2335 (Online)

The genetic defect in LND lies in an enzyme of purine metabolism Hypoxanthine—Guanine Phosphoribosyl Transferase (HPRT). Not all boys with HPRT deficiency have LND, there are 3 intermediate forms called LND variants, all of which have varying but milder neurological symptoms. The fifth is called partial HPRT deficiency, or Kelley–Seegmiller syndrome, where no neurological symptoms are found.

The diagnosis depends upon the clinical signs and symptoms and correct metabolic investigations. In the baby the clinical signs are developmental delay, hypotonia, irritability, feeding difficulties and 'sand' or orange crystals in the in diaper. Sometimes kidney failure occurs precipitated by infection. In the older child a diagnosis of athetoid cerebral palsy might be made but excessive crying and biting the lips or fingers may also be noticed.

BIOCHEMICAL INVESTIGATIONS IN LND

The level of uric acid in blood plasma and urine will be raised and the plasma uric acid creatinine ratio raised 2–4 fold, compared to healthy boys of the same age. It is important to know that renal clearance of uric acid in children is higher than in adults, so the plasma uric acid may not be raised but the urine will show grossly elevated levels. The diagnosis depends upon measurement of HPRT activity. Referral should be made to a specialist centre aware of the many pitfalls involved. HPRT must be measured in both disrupted and intact blood cells and sometimes from fibroblasts cultured from skin biopsy. LND patients have virtually no detectable HPRT activity in any cell type.

RADIOLOGICAL DIAGNOSIS

Ultrasound examination of the kidneys may give the first clue to diagnosis. Renal failure may occur in baby boys with HPRT deficiency often precipitated by urinary tract infection. Early diagnosis is important so that appropriate management can be started. This benefits the baby and parents and may prevent the birth of another affected child by promoting genetic counselling for family members.

NEUROLOGICAL PROBLEMS IN LESCH NYHAN DISEASE

The areas of neurological involvement are:—motor disorder, which evolves from hypotonia into dystonia or choreoathetosis and spasticity; bulbar symptoms occur early and affect feeding and later speech development; compulsive self-injurious behaviour and aggression; and cognitive impairment.

HPRT activity in the brain is highest in the basal ganglia, where it is believed to be necessary for DNA, RNA and protein synthesis. Neuroimaging studies have shown that the brain is generally smaller in people with HPRT deficiency.[1–2] Also the size of the caudate and putamen are reduced in LND subjects and PET scanning has shown that dopamine transporter density is also reduced, this correlates with the motor disorder but does not explain the self-injurious behaviour and aggression.[3]

It has been postulated that the absence of HPRT impairs the normal dendritic arborisation of dopamine fibres through impaired neurotransmission. However, research with a strain of HPRT deficient mice failed to confirm this finding and other factors such as oxidative stress or altered expression of other genes are being examined.

The Dystonia Medical Research Foundation defines dystonia as a syndrome of sustained muscle contractions, frequently causing twisting or repetitive movements or abnormal postures. It affects the facial muscles and impairs speech, swallowing, and gross movements. The degree of motor disorder is variable, some boys develop good motor control but in the majority the extreme torsion spasm and self-injury make weight bearing or independent walking impossible. However, it is important to give plenty of motor stimulation and encouragement and to use appropriate walking aids and equipment for standing to encourage independence. Early seating support will enable hand control to develop and the use of a tray with guard will prevent toys from falling too easily. A programme of posture management is recommended to prevent fixed deformities developing around the hips and spine. This includes night-time positioning if the posture is distorted.

Speech and Communication—The baby with LND needs to be seen by a Speech and Language Therapist skilled in management of young children with cerebral palsy. The first task is to help with eating and drinking. This moves on naturally to the development of early communication skills and play. Feeding difficulties may be associated with the development of a hiatus hernia. There may be vomiting, chest pain, bleeding and sometimes inhalation into the lungs. Acid reflux can also occur without a hernia. Vomiting or spitting can be used by some boys as aggressive acts. Severe complications can occur in this condition so it is important to investigate and treat actively. Sometimes surgical treatment is required. The speech muscles are affected by dystonic spasm causing slurring of speech sounds particularly under stress. Stress management by parents and carers is essential in the early years and later it is helpful to teach relaxation techniques to the boys. An alternative communication system may be necessary to reduce stress. For example using pictures or symbols initially and later moving on to technical devices.

A **Multidisciplinary Team Approach** is helpful in the management of LND. Our experience at Chailey Heritage has shown the benefit of involving the skills of rehabilitation engineers, occupational and physiotherapists, speech and language therapists, teachers and carers as well as psychologists, nurses, doctors and social workers. This may seem a huge number of people but it is important to understand the natural history of the condition and it can be immensely rewarding to put our heads together with the child and family to problem-solve. The aim is always to facilitate the development and health of the child and enable him to reach his potential.

Aids to daily living are essential including suitable bath and toilet seats, special hoists for older children and suitable padding to beds and other hard surfaces. Standing and walking aids may be necessary. Boys also enjoy adapted cycles. Wheelchairs may also require postural support equipment. A powered chair with a Sensor Collision Avoidance Device may also be helpful. This is a system for steering guidance along corridors, through doorways or anywhere with well-defined borders, significantly reducing the risk of collision. Switches can be used for driving and also for play with electrically driven toys.

Medical Treatment *Allopurinol* lowers the uric acid level in the blood, thus preventing kidney stones and gout. The dose needs to be carefully monitored as in

excess Xanthine excretion may rise and cause stones instead. *Potassium Citrate mixture* makes the urine alkaline and increases solubility of uric acid. A high fluid intake is also recommended. It should be noted that some drugs called 'uricosuric agents' interact with Allopurinol and increase the delivery of uric acid to the kidneys and risk acute crystal deposition causing discomfort or pain. These include Ampicillin and Amoxicillin. It is important to check for this interaction when new medicines are prescribed.

Adequate pain control is important when injury occurs to prevent a vicious circle of pain and injury. Spasm and anxiety may be reduced by the use of *Diazepam* but dependency may develop. *Baclofen* reduces muscle spasm the dose should be adjusted to give maximum effect avoiding side effects.

There is no one drug that we know will be helpful to treat the movement disorder in all cases, *L dopa, Tetrabenazine* and other drugs may be tried.

Drug treatment of self-injurious behaviour is also difficult. *Diazepam, Valproate, Carbamazepine, and Gabapentin* have all been used with variable success. Behavioural management is usually most successful although medication may be required for short periods.

Sleep problems are common in LND. Parents report a high level of sleep problems including difficulty getting off to sleep, noisy breathing and 'sleep apnoea.' Posture during sleep may cause injury, especially extreme neck extension and various solutions have been found to improve sleeping positions. Nocturnal video observation may be useful.

Day time apnoea can also occur triggered by acid reflux from the stomach with inhalation, epilepsy and neck extension causing the blood supply to the back of the brain to be reduced.

Growth and Puberty from birth there is slow weight gain, probably multifactorial but it could be due to failure of cellular function. Testicular atrophy has been found at autopsy in several boys, the absence of the normally high HPRT activity in the testes may inhibit the response to gonadotrophin.[4]

In the first year of life growth may be affected by feeding difficulties and stomach problems. Although most of the uric acid excreted arises from the metabolic defect, the use of a low purine, low caffeine diet is recommended. This reduces the total uric acid load to the kidney and avoids peaks that may cause pain and irritability.

Behaviour and Cognitive problems. A comprehensive study of neuro-cognitive function comparing 15 LND subjects, to 9 LND variants and 13 normal adolescents and adults was published in 2001.[5] Testing revealed unambiguous and qualitatively similar cognitive deficits in both LND subject groups. The variants produced scores that were intermediate between those of subjects with LND and normal controls in every cognitive measure.

Other investigations were also carried out on the HPRT deficient subjects including neuroradiological assessments MRI and PET.

In summary the LND and Partial HPRT subjects showed relatively mild impairment of temporal lobe orientation and recognition memory, severe impairment of auditory divided attention and free recall on word list learning and moderately severe impairment on tests of reasoning and intelligence.

Self-Injurious Behaviour (SIB) is often the most distressing aspect of LND for the boys and parents and carers. It can be defined as any behaviour initiated by the individual, which directly results in physical harm to that individual. SIB occurs in 85% of cases of LND it can start at any time, on average at 3 years. It is compulsive and distressing and appears to be biologically driven.

Management depends on teaching good communication skills, relaxation techniques and consistent handling by family, teachers and carers.

Protective devices are necessary when SIB is severe. These include padding of bedsides, wheel chairs, helmets, gloves, arm splints, gum shields, 'super-market straps,' waistcoats for sleeping. Although these devices are necessary, it is wise to try to encourage the boys to self-restrain e.g. tucking arms into belts or sitting on their hands.

In a study reported in 2003, data were collected from 64 families with LND members in the USA and abroad.[6] The individuals ranged from 1 to 40 years, 1 female. Biting lips or fingers, 53%, was the commonest initial mode of SIB, 48% had oral or facial damage, 25% damage to hands, and 42% had some or all teeth removed. Other behaviours included head banging, extension of arms through doorways, tipping wheelchairs, eye poking, fingers in wheelchair spokes, and rubbing ears or nose. Verbally abusive behaviour or spitting at others was characterised as emotional self-injury.

Hierarchical cluster analysis found evidence of patterns in the self-mutilating behaviours of individuals. There are changes in sets of behaviours over time with additions of new behaviours or cycles back to old behaviours persisting into adulthood. Outwardly directed behaviours occur which were characterised as emotional self-injury.

Life expectancy is reduced in LND, although some men have lived into their forties, death usually occurs earlier from a variety of causes: renal failure in young boys who may present with renal damage; sudden unexpected death in boys who may have apnoeic attacks or inhalation from reflux and hiatus hernia; gradual deterioration with bulbar symptoms and death from respiratory failure. Depression is common and may require medication.

THE NEED FOR RESEARCH

The predicament of boys with Lesch Nyhan Disease, and their families, is great. Their condition is rare and the diagnosis is often delayed. Education of clinicians, teachers and therapists takes time. The Lesch–Nyhan Children's Research Foundation in the USA has an impressive record of collaborative research. It was set up in Illinois by parents of affected sons in 1994 to raise funds to promote research, study and other programs in support of children with Lesch Nyhan Syndrome. The collaborative approach is mirrored in the UK by the Purine Metabolic Patients Association (PUMPA) set up in 1991 to promote research into the purine disorders by Dr Anne Simmonds and her colleagues at Guys Hospital Purine Research Unit. The Princess Margaret Nucleotide Metabolism Centre has been set up following a recent EC 'Orphan Diseases' grant involving researchers in 19 countries in Europe. A Virtual Centre is envisaged its core will be the Purine Research Unit at Guy's Hospital, London.

ACKNOWLEDGMENTS

I would like to acknowledge the support of Dr James Harris and Dr Anne Simmonds, Dr Lynette Fairbanks and Dr John Duley from the Purine Research Unit, Guy's Hospital.

REFERENCES

1. Harris, J.C.; Schretlen, D.; Bryan, N.; Wong, D.F. Magnetic resonance imaging in Lesch–Nyhan disease: correlation of caudate nucleus volume and cognitive functioning. Society for Neuroscience Abstracts **1996**, *22*, 265.
2. Harris, J.C.; Lee, R.; Jinnah, H.A.; Wong, D.F.; Yaster, M.; Bryan, R.N. Craniocerebral Magnetic Resonance Imaging measurement and findings in Lesch–Nyhan Syndrome. Arch. Neurol. **1998**, (55), 547–553.
3. Harris, J.C.; Wong, D.F.; Jinnah, H.A.; Schretlen, D.; Yorkoi, F.; Stephane, M.; Dogen, S. Dopamine transporter binding of WIN35,428 correlates with HPRT level and extent of movement disorder but not with self-injurious behaviour. In *Abstracts Society for Neuroscience Annual Meeting*; PUMPA and Chailey Heritage Clinical Services: Miama, Florida, 1999; (No 855.9).
4. Watts, R.W.E.; Harkness, R.A.; Spellacy, E.; Taylor, N.F. Lesch Nyhan Syndrome: growth delay, testicular atrophy and a partial failure of the 11 beta-hydroxylation of steroids. J. Inherit. Metab. Dis. **1987**, *10*, 210–233.
5. Schretlen, D.J.; Harris, J.C.; Park, K.S.; Jinnah, H.A.; Del Pozo, N.O. Neurocognitive functioning in Lesch–Nyhan Disease and partial hypoxanthine-guanine phosphoribosyl transferase deficiency. J. Int. Neuropsychol. Soc. **2001**, *7*, 805–812.
6. Robey, K.F.; Reck, J.F.; Giacomini, K.D.; Barabas, G.; Eddey, G.E. Modes and patterns of self-mutilation in persons with Lesch Nyhan Disease. Dev. Med. Child Neurol. **2003**, *45*, 167–171.