The history around a genetic condition from demon possessed to Lesch-Nyhan disease

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INTRODUCTION

Lesch–Nyhan disease (LND), is a rare inherited metabolic disorder caused by deficiency of the enzyme hypoxanthine guanine phosphoribosyltransferase (HPRT). It is caused by mutations involving the HPRT1 gene located on the X chromosome.

Fig.1The locus of HPRT1 on the X chromosome

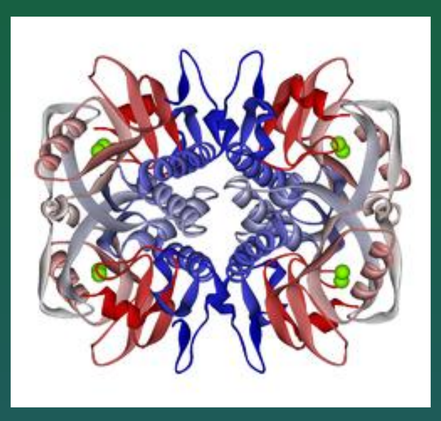

Fig.2 Ribbon diagram of a human HPRT tetramer.

LNS affects about one in 380,000 live births. The disorder was first recognized and clinically characterized by medical student Michael Lesch and his mentor, pediatrician Bill Nyhan.

LNS is characterized by three major hallmarks: neurologic dysfunction, cognitive and behavioral disturbances including self-mutilation, and uric acid overproduction (hyperuricemia). Damage to the basal ganglia causes sufferers to adopt a characteristic fencing stance due to the nature of the lesion. Some may also be afflicted with macrocytic anemia. Virtually all patients are male; males suffer delayed growth and puberty, and most develop shrunken testicles or testicular atrophy. Female carriers are at an increased risk for gouty arthritis but are usually otherwise unaffected.

THE STORY

A young boy speaking in an incomprehensible manner, using foul words, moving with sudden and incontrollable movements, aggressive towards others and self-mutilating his body. Add to this terrible image the fact that this boy has to be bound to his bed to prevent him from hurting himself or others. There is little doubt that centuries ago this kind of a description would only fit a case of demonic possession and the restraints would be there to prevent the demon from doing harm.

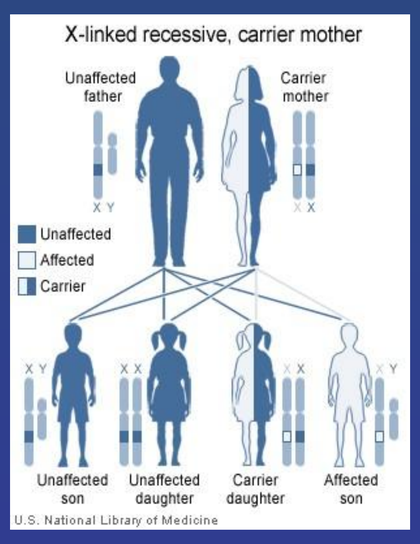

Fig.3 LNS is inherited in an X-linked recessive fashion.

In 1963, a 4 years old boy with a similar story came to the attention of paediatrician and biochemical geneticist William Leo Nyhan and his student Michael Lesch at the John Hopkins Hospital. His terrible story had two distinctive additional features; he had uric acid crystals in the urine and a 4 years older brother with the same condition. The two brothers led to a scientific description of the condition and it became an X-linked recessive disorder with progressive mental retardation and a bizarre tendency to self-mutilation. Henceforth this condition became also known as Lesch-Nyhan disease (LND). It took less than three years for dr. Jarvis Edwin Seegmiller and his colleagues to identify that LND was due to the deficiency of the enzyme hypoxanthine guanine phosphoribosyltransferase. Science required several years until the gene encoding the human enzyme could be cloned and sequenced. Theodore Friedmann and colleagues unravelled the code of the HPRT1 gene in 1985.
1966 was the year that gave the condition its first treatment that would dramatically improve the patients' quality of life. The drug used was allopurinol, a purine analog capable of inhibiting the enzyme xanthine oxidase that converts xanthine into uric acid. Sadly this treatment would be limited to the direct effects of hyperuricaemia, namely a very severe form of gout, but wouldn't allow any improvement of the "demonic possession".
Time passes and Lesch-Nyhan disease has undergone a dramatic change over time. Today we know the "demon" and know how to deal with some aspects of its "possession". We learned that the gout caused by HPRT deficiency isn't like the "rich men" gout and that low purine diets not only aren't useful but can harm the boys.
We know so much now yet we are still struggling to find the correct "exorcism" to banish LND forever from our affected boys.

TREATMENT

Treatment for LNS is symptomatic. Gout can be treated with allopurinol to control excessive amounts of uric acid. Kidney stones may be treated with lithotripsy, a technique for breaking up kidney stones using shock waves or laser beams. There is no standard treatment for the neurological symptoms of LNS. Some may be relieved with the drugs carbidopa/levodopa, diazepam, phenobarbital, or haloperidol.

B.I.R.D. and LND

"Mauro Baschirotto" Institute for rare diseases is deeply committed to LND by offering molecular diagnoses, treatment supervision and advanced research on the molecular bases of the disease. Our services are extended not only to national but also to international cases. The diagnoses offered are based on several methods spanning from gDNA sequencing to cDNA sequencing, from CNV to deleion mapping; both for postnatal and prenatal testing. We dicovered the etiopathogenic cause of disease in more than 50 unrelated families including carrier testing and prenatal dignoses.