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

INTRODUCTION

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

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 uncontrollable 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.

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 hyperuricemia, 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 Baschirrrotto” 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 discovered the etiopathogenic cause of disease in more
than 50 unrelated families including carrier testing and prenatal diagnoses.