MODELS OF INTEGRATIVE APPROACH IN DIFFERENT RARE DISEASES

Prader-Willi Syndrome and Lesch-Nyhan Disease

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“Mauro Baschirotto” Institute for Rare Diseases – B.I.R.D. Foundation NPO
Fourth Eastern European Conference for Rare Diseases and Orphan Drugs
“Together for Integrative Approach to Rare Diseases”
13-14 June 2009 - Plovdiv, Bulgaria
B.I.R.D. Foundation Europe NPO

Genetic diagnostics
- Molecular
- Cytogenetic

Research
- Advanced diagnoses
- Therapy and treatment
- Population studies
- Basic research

Rehabilitation
- Physiotherapy
- Occupational therapy
- Music Therapy
- Many more

Clinical Centre
- Plurispecialistic medical examinations
- Ecography
Prader – Willi Syndrome (PWS)

- **Prevalence:** 1:20,000

- **Disease characteristics:**
  - Caused by the loss of paternal imprinting within the Prader-Willi critical region (PWCR) in 15q11.2-q13
  - Patients have severe hypotonia, feeding difficulties with failure to thrive in early infancy, hyperphagia occurring in early childhood, cognitive impairment, a distinctive behavioral phenotype with temper tantrums, stubbornness, manipulative behavior, and obsessive - compulsive characteristics, hypogonadism with genital hypoplasia, incomplete pubertal development, and, in most, infertility. Short stature is common; characteristic facial features, strabismus, small hands and feet, scoliosis are often present, and non-insulin-dependent diabetes mellitus often develops in obese individuals.
B.I.R.D. and PWS

• The foundation wants to be on the family’s side; helping diagnose, understand and manage their condition
• For PWS the institute offers:
  • Clinical diagnosis
  • Molecular diagnosis (MS PCR, MLPA, FISH, STR)
  • In patient adult PWS rehabilitation cycles
  • Medical counseling
  • Psychological support
  • Rising awareness of PWS
  • Research
Gunay-Aygun (2001):

- **Birth to two years:**
  - Hypotonia with poor suck in the neonatal period
- **Two to six years:**
  - Hypotonia with history of poor suck
  - Global developmental delay
- **Six to 12 years:**
  - History of hypotonia with poor suck
  - Global developmental delay
  - Excessive eating with central obesity if uncontrolled
- **13 years to adulthood:**
  - Cognitive impairment, usually mild mental retardation
  - Excessive eating with central obesity if uncontrolled
  - Hypothalamic hypogonadism and/or typical behaviour problems
PWS molecular diagnosis

• Molecular diagnosis:
  – MS MLPA (det. rate 99%, gDNA level)
  – MS PCR (det. rate 99%, gDNA level)
  – STR (det. rate 25%; gDNA level, requires parents)
  – FISH (det. rate 70%; requires cells)

• Floppy infant screening:
  – PWS is one of the causes of this condition with an incidence of 5-10% of the floppy infants
  – The MS PCR test is performed at the fifth day of life and referral time is within the 24 hours
B.I.R.D. International PWS Diagnoses

Diagnoses 2003-2009: 270 PWS from all over the world
The adult PWS rehabilitation:

• **Must be a collaboration including the family, healthcare personnel, caretakers and all other persons that are in contact with the patient**

• **Besides hormonal therapies and continual medical support, optimization of the diet is essential, together with careful planning of the social, and physical activities, as well as fixing simple rules they can follow**

• **Therapy must start at birth and follow the patient in adulthood**

• **Rehabilitation cycles can be of great aid to the family in following these goals**
Objectives of the PWS therapeutic cycles:

- **Help in weight control and better management:**
  - Diet
  - Physiotherapy, psychomotor therapy, occupational therapy, recreational therapy
  - Socializing
  - Check of general health status during stay

- **Help families:**
  - Lightening their amount of work; offers some relief during the cycle
  - Creating a management schedule; loss of weight and rehabilitation

- **Integration into routine therapeutic activities**
Reaching the objectives

- Cycles for in patient diagnosis - rehabilitation of 2 - 4 weeks are organized for groups of 6 - 10 PWS patients with medical and rehabilitative equipment and several specialists (endocrinologist, physiatrist, pediatrician, psychiatrist, oculist, dentist, neurologist, neuropsychologist, nutritionist, physiotherapist, psychomotor therapist, educators)
- Medical check up is performed (hematological, ultrasound testing as well as neuropsychological tests, qualitative and quantitative body composition analysis and more)
- PWS tailored Mediterranean diet (1500 kcal/die)
- Physical activity
- Physiotherapy
- Leisure and social activities (singing, dancing, drawing, music, table games, excursions)
Did we succeed?

Mean weight loss in function of the days of therapy for the PWS cycles 2002-2009
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Lesch Nyhan Syndrome (LNS)

- **Prevalence:** 1:380,000

- **Disease characteristics:**
  - Caused by a hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency, a purine metabolism enzyme: the gene encoding this protein is located on chromosome X in position Xq26-27.2
  - Patients have uric acid hyperproduction, neonatal hypotonia, developmental delay, dystonia, choreoathetosis, opisthotonos, spasticity, hyperreflexia, and extensor plantar reflexes.
  - Pathognomonic is the selfmutilating behaviour called Lesch-Nyhan behaviour
  - Patients often develop a megaloblastic anemia
B.I.R.D. and LNS

• The foundation wants to be on the family’s side; helping diagnose, understand and manage their condition

• For LNS the institute offers:
  • Clinical diagnosis
  • Molecular diagnosis (gDNA sequencing, cDNA sequencing, qPCR, exon exclusion specific cDNA PCR*, deletion gDNA breakpoint determination*)
  • Genetic counseling
  • Psychological support, therapy coordination
  • Rising awareness of LNS
  • Research activities, clinical trials
Clinical diagnosis of LNS

- The diagnosis of LNS is suspected in males with hyperuricemia and developmental delay during the first year of life.

- The diagnosis is enforced in the presence of the characteristic neurologic, cognitive, and behavioral disturbances.

- The presence of LN behaviour is pathognomonic.
## Molecular diagnosis of LNS

<table>
<thead>
<tr>
<th>Method</th>
<th>Patients</th>
<th>Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>gDNA sequencing</td>
<td>94%</td>
<td>69%</td>
</tr>
<tr>
<td>cDNA sequencing</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>qPCR</td>
<td></td>
<td>25%</td>
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<tr>
<td>ees cDNA PCR</td>
<td></td>
<td>6%</td>
</tr>
</tbody>
</table>

*(B.I.R.D. 2009 unpublished)*
LNS therapy today

- **Allupurinol**

  ![Allupurinol structure]

- **Rasburicasi (Fasturtec)**

  ![Rasburicasi structure]

\[
\text{Uric acid} + O_2 + H_2O \rightarrow 5\text{-hydroxyisourate} + H_2O_2 \rightarrow \text{allantoin} + CO_2
\]
HPRT Pathway
SAME in LNS - Clinical Trial

- Started in 2008
- Recruited 29 LNS patients
- Protocol is a crossover study during 12 months
- Dosages were adjusted by renal function
- Currently ending observation phase
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LNS Conferences

8th Lesch – Nyhan Family Meeting
June 19th – June 21st 2009

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Worldwide mission

The foundation wants to offer free of charge molecular diagnoses to anyone that requires it for:

- Prader – Willi Syndrome / Angelman Syndrome (MS PCR)
- Lesch – Nyhan syndrome (HPRT1 gene)
- Autoimmune Polyendocrine Syndrome Type 1 (AIRE gene)
- Krabbè Leukodystrophy (GALC gene)
- Metachromatic Leukodystrophy (ARSA, PSAP genes)

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