Workshop: Patient Databases and Registries

Input of families into the database
« International Rett Syndrome »

Gerard NGUYEN
Rett Syndrome Europe

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The patients’ voice: « Involvement of patients and PO... »

In a perfect technically controlled « world »

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Rett Syndrome

- A rare disease (1/20,000 girls)
- Severe Neurodevelopmental disorder with multiple handicap
- Affecting girls (X linked),
- Mutation MeCP2
- High level of dependency
Fundamental needs

Complete dependence: daily activities (%)

- Self care: 97.7%
- Bathing: 97.7%
- Eating: 83.7%
- Dressing waist down: 100%
- Dressing waist up: 97.7%
- Toileting: 98.8%

H Leonard, 2001
Relation function
Partial dependence : (%)
Rett Syndrome: 1960 to 2009

- 1960: first description by Pr Andreas Rett
- 1988: Consensus on definition (Clinical Criteria (Bengt Hagberg))
- 1999: Discovery of the mutation: gene MeCP2
- 2002: Mouse Models (Adrian Bird)
- 2009:
  - Multiple treatment options: Phase II-III CTs
  - Multiple data bases, registries, research networks

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## Rett Syndrome Data Warehouse!

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<th>Worldwide</th>
<th>Europe</th>
<th>USA</th>
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<tbody>
<tr>
<td><strong>Clinical Research Networks</strong></td>
<td>RettSearch</td>
<td>EuroRett</td>
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<td><strong>Basic Research Networks</strong></td>
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<td>EuroRett</td>
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InterRett

- International project to collect information about individuals diagnosed with Rett syndrome

- Funded by IRSF - International Rett Syndrome Foundation (USA) (families’ organisation)

- Managed by the Australian Rett syndrome team based Perth (academic, hospital)

- Commenced in 2002
Objectives

1. Provide a large sample of cases for analysis

2. Provide an innovative and efficient mechanism to disseminate information

3. Encourage collaboration around the world
   1. Families
   2. Researchers
   3. Physicians
   4. Carers
Objective 1

1. Provide a large sample of cases for analysis - why?
   To increase statistical power
Provide a large sample

• Studies are limited by the number of cases available on a national level

• Diversity of Health systems, and care organisations

• Even more so if they are investigating specific mutations or characteristics

• Solution is to pool data from multiple countries
Objective 1

1. Provide a large sample of cases for analysis - how?

Invite families to participate
  • Website
  • Family associations

Family provide Consent
Complete questionnaire
(online/paper-based)

Invite a clinician to provide
clinical information
Objective 1: data input
data coming from 2 sources

Family information (individual families)
Total (623)

- Family data only 346
- Clinician data only 152
- Family & clinician 277
- Spanish 354
- French 231
- Australia 331
- Total 1,691

Clinical Information (Total 429)

- From clinicians with one or a few patients (152)
- From clinicians with large datasets (916)

Both family and clinical information 277

Spanish data (Dr Pineda’s questionnaire)

French data Coded (Adaptation of InterRett questionnaire)

Australian data (Australian questionnaire)
Other = countries with 10 or less participants:

Argentina, Austria, Belgium, Bolivia, Brazil, Chilie, Columbia, Denmark, Germany, Honduras, Hungary, India, Iran, Ireland, Italy, Japan, Malta, Mexico, Netherlands, New Zealand, Norway, Peru, Portugal, South Africa, Sweden, Switzerland, Taiwan, Turkey, United Arab Emirates, Uruguay

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### Outcomes

#### Mutation test

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Total</th>
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<tbody>
<tr>
<td>Positive</td>
<td>1010</td>
<td>316</td>
<td>157</td>
<td>1483</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Uncertain</td>
<td></td>
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#### 652 with common mutations

**Mecp2 mutation is not a diagnosis criteria**
Welcome to the InterRett Output Database

This is a searchable database which allows you to create graphs based on the information provided in the InterRett family questionnaires from families around the world.

Create a graph of one variable

Select a single variable →  Create graph

OR Compare two variables

Distribution of 7 most common mutations  By  Walk unaided
Objective 2

2. Provide an innovative and efficient mechanism to disseminate information - why?

Increase the clinical understanding of Rett syndrome
- Natural history of the disease (from diagnosis to death)
- Description of early symptoms (before diagnosis)
- Description of mutations
- Relation Genotype-Phenotype +++
- Level of dependency
- Quality of life scale

Maximise the use of information collected
Objective 2

Publications

  Investigating genotype-phenotype relationships in Rett syndrome using an international dataset.

  The diagnosis of autism in a female: could it be Rett syndrome?

  Lost in translation: translational interference from a recurrent mutation in exon 1 of MECP2
Objective 3: Management Guidelines

- **Scoliosis guidelines** *(Clinical management)*
  - Using the Internet to build consensus
  - Meaningful results from a simple infrastructure
  - Approach can be applied to other research objectives
Researchers’ conclusions

• Data sharing makes sense
  – Improved statistical power
  – Avoids duplication of effort
  – Reduces burden on families
  – Reduces cost to funding bodies

• Challenges
  – Need to protect patient privacy
    • Informed consent
  – Intellectual property rights of researchers
    • Collaborate but remain competitive
  – Lack of standardisation
Researchers’ conclusions: The way forward

• We need consensus on how to proceed
• Establish common protocols
• Take stock
  – Why and when we should pool data
  – Identify all the data sources available
  – What can be shared and what can’t
  – Avoid duplications
www.eurorett.eu
<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>INSTITUTIONS</th>
</tr>
</thead>
</table>
| Germany | Projekträger im Deutschen Zentrum für Luft- und Raumfahrt  
Bundesministerium für Bildung und Forschung |
| Spain   | Fundación para la Cooperación y Salud Internacional  
Instituto de Salud Carlos III |
| France  | Agence Nationale de la Recherche, GIS Institut des Maladies Rares |
| Israel  | Chief Scientist's Office, Ministry of Health |
| Italy   | Istituto Superiore di Sanità |

Grant awarded: € 1,400,000 / $ 2,000,000

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EuroRett
Funded by E Rare (ERA Net, FP7)

To build a european database and patients’ registry
To improve genotype/phenotype correlations
To study Mecp2 function
To understand neuronal dysfunction
To develop therapeutic approaches

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EuroRETT Consortium Research Network
## EuroRETT : PO support

### PARENTS & FRIENDS OF PATIENTS

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<thead>
<tr>
<th>Country</th>
<th>Organization</th>
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<tbody>
<tr>
<td>Germany</td>
<td>Elternhilfe für Kinder mit Rett-Syndrom in Deutschland e.V.</td>
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<tr>
<td>Spain</td>
<td>Associació Catalana de la Síndrome de Rett</td>
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<tr>
<td></td>
<td>Asociacion Valenciana Sindrome de Rett</td>
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<tr>
<td>Europe</td>
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<tr>
<td>France</td>
<td>Association Française du Syndrome de Rett</td>
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<td>Israel</td>
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<tr>
<td>Italy</td>
<td>Associazione Italiana Rett</td>
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<td>ProRETTricerca.</td>
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</table>
PO support!

« We very much appreciate that through this E-RARE application, EuroRETT, the research on Rett syndrome in Europe is becoming a joint effort. »

« (…) the unanimous view of all the countries present was to support such a worthwhile project (…) »

« We express the wish that such a network has all the capacities to work in Europe for the entire benefit of a possible cure and care of our children. »

« We hope that E-RARE projects would be a starting point for more and more cooperation between researchers from different countries(…) »

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Am I happy?

1) Data Base and registries
   - responding to most of EPPOSI recommendations
   - consent form
   - Public funds

2) Global outcomes reached
   - better understanding of the disease
   - Severity factors, (Genotype-phenotype)
   - Drug development
   - International collaborations

3) Patients’ and families’ involvement
   - co-funding
   - data input
   - PO visibility

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A success story?
What is the question?

- Registries in RD, for research and drug development?
- Parents’(patients’) involvement?
  - The role
- Call for action?
- To respond to our challenge (EURORDIS): patient empowerment?
The answerable question?
Parents’ (patients’) involvement

Photo AFSR

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The child’s rights

I am not

Your author

Your advocate

Your representative

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Real Life versus Controlled research situations

Population having the RD x

Registries

CT
Registry: participants’ point of view (1)

- Guinea pig or patient
- Altruism > personal benefits
- Should be able to select the level of involvement using levels of consent
  - Attitudes: more relaxed, degree of openness
  - Range of levels of consent: at selection and depending on the future use by researchers
- Access to the registry:
  - Physicians are more cautious
  - Patients’ concerns: marketing agencies, employers, insurance, pharmas
  - Guardianship of data

W Baird, J Med Ethics 2009
Registry: participants’ point of view (2)

• Balancing Privacy and Scientific Issues
  – Invasion of privacy
    • Harms: misuse of medical information
    • Wrongs: violation of person respect

• Confidentiality, Consent and access

• Retention and maintenance

• Patient education (active and passive)

• Involvement of treating physicians
  – Notification > permission

Laura M Beskow, AJM 2006

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Patients’ barriers

- 40% of patients did not understand the idea of a research
  - Understandable information

- 45% indicated that patients in CTs are « treated as guinea pigs »

- 84% CTs may provide « better initial treatment »

- 75% CTs were associated with « high quality medical care »

- 40% of new cancer patients qualified for CTs decline to participate

R.L. Comis, J Clin Oncol 2003
Patient satisfaction

- Evaluation of informed consent procedure
- Attitudes on medical research and care
- Expected benefits
  - Of the trial
  - Medical treatment, care
- Expected disadvantages
- Health locus of control
- Health and illness perceptions
- Patient background characteristics

F.W.S.M. Verheggen, Int J for quality in Health Care, 1998

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Understandable information in the context of Patient-physician communication

Mean duration 92 seconds and 78% expressed their needs less than 120 seconds

Physicians interrupt their patients’ expression after 22 seconds

BMJ 2002, 325: 682-683

JAMA 1999, 281: 283-287

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Remodelling
the approach of research

Medical Model

Social research

Social Model

Empowerment
Access

Health priority

Disease
Care
Cure
Education
Patient centred

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Health belief model

Psycho-sociological factors

Beliefs on benefits minus Beliefs on barriers

Faiths on his (her, its) vulnerability in the disease and its gravity

Faiths on the threat which represents the disease

Credibility that we adopt the behavior

Signal

Disease
Care, cure
Research
- Registries
- Clinical trials

Adapted from MH Becker
The burden of the disease: family mapping

Nature of reactions

- Attitudinal
- Contextual
- Normative
- Behavioural

Source of reactions

The Neurotic Parent
Psychodynamic Orientation
Inevitable parental neuroses
- Guilt
- Anger
- Denial
- Grief

The Suffering Parent
Psychological Orientation
Situational parental feelings
- Chronic sorrow
- Novelty shock
- Isolation/loneliness
- Stress

The Dysfunctional Parent
Behavioural Orientation
Predictable parental dysfunction
- Role disruption
- Marital disruption
- Social

The Powerless Parent
Sociocultural Orientation
Situational parental behaviour
- Fatigue (from poor)
- Impoverishment
- Stigma
- Powerlessness

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P.M. Ferguson, Mapping the Family
Real Life: Stress and adaptation

Intrafamily Resources +/-

Community Resources (-)

Stressor (Burden)

Family Appraisal and Coping Responses

Positive Adaptations

Negative Adaptations

Singer and Irwin, 1989:6

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RD, Registry, CT, PO management
Proposals to be discussed

• 1) How to improve and implement active patient participation?
  – Involvement +++ in:
    • Working groups on registries and CTs
    • Institutions preparing, validating, disseminating guidelines
    • Boards and Committees (oversight)
    • Design, document validation, production
  – PO member registry: biased source for patient selection?
  – Recruitment, retention (duration of the register)
  – Patients’ discomfort (additional discomfort: time, tests, costs…)
  – National vs International registries

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Proposals to be discussed

• 2) How to improve information at participation?
  – Information for selection
  – Quality chart (score) at selection
  – Understandable Informed consent
  – Information tools, methods
  – Patient education and training (benchmark: Eurordis summer school)
Proposals to be discussed

3) Rethinking the partnership on a win win basis
   - Defining outcomes: Quality of Life, patients’ satisfaction, cost effectiveness, quality of care
   - Multiple purposes, involving all stakeholders (inclusion of expertise) in the preparation
   - Needs to develop social and economic research
   - Needs to create registries involving patients…
     • WP (led by PO) in any research project in EC call
     • Involvement of PO or patients as an « impact criteria » for FP reviewers in the call selection
     • In any research network
     • In any CT
The children’ expectation?
Quality of Life

Definition

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In the Land of Hippocrates, Socrates...
Take home message: data...our biography, our history of life...the heritage
For social ritual rebuilding

Their eyes speak, I am sure that they understand everything...Andreas Rett
The first says "Sawubona" "I see you, "
The other answers "Sikhona" "I am here,"

Unbuntu philosophy "Umuntu ngumuntu nagabantu",
in Zoulou

"A person is a person by other persons"
Comment se quitter sans pleurer
“Umuntu ngumuntu nagabantu”
Dans le pays Natal
Selon le rituel Zoulou…
Il y a Toi Toi Toi et Moi et Moi et Moi… émoi
“Sawubona”
“Sikhona”
“Sikhona”
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