Recessive spastic paraplegias

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Recessive spastic paraplegias

- They are far less represented in your associations.
- And yet they stand for an important part of spastic paraplegias,
- and affected families may be in a greater need for help, support and company.
- It is, I think, high time to talk about them.
My interest in recessive spastic paraplegias

- When I began Neurology, even when I became involved with genetic diseases of the NS,
- hereditary spastic paraplegias, and particularly recessive spastic paraplegias, were always placed at the end of the chapter, in small letters at the bottom.
Through an epidemiologic study of hereditary spastic paraplegias in Portugal we collected, a considerable number of patients in a considerable number of families (about 120 kindreds) affected by recessive spastic paraplegias.
We first tried to separate them in pure and complex (as for dominant families),
but this didn’t not work well:
- in the same kindred you often have pure and complex forms,
- and pure forms may turn complex with time.

Besides, genes first described as linked to pure forms correspond to complex patients, at least in our Portuguese families.
Recessive spastic paraplegias in Portugal 1994

- Pure, early-onset
- Spastic ataxias
- With mental retardation
- Miscellanea
- Pure late-onset
Why interested, at last?

- Because, at last, they began to make sense in my head.

How?

- Finally, a particular form of recessive spastic paraplegia was reported in Japan.
Iwabuchi: association of spastic paraplegia, mental retardation, "hypoplasia" of the corpus callosum 1994

SPG11 15q13-q15
Martinez-Murillo
Mental retardation, thin corpus callosum 1999

SPG15 14q22-q24  Kjellin syndrome
Kjellin (Hughes, 2001) thin corpus callosum
Mental retardation, macular degeneration, hand amyotrophies 1959
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Chromosome</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Troyer syndrome</strong></td>
<td>13q12.3</td>
<td>Small stature, mental retardation, neuropathy onset in childhood, thin corpus callosum</td>
</tr>
<tr>
<td><strong>Mast syndrome</strong></td>
<td>15q22.31</td>
<td>Early adulthood, cognitive decline, Older Amish, thin corpus callosum</td>
</tr>
</tbody>
</table>
The “Thin Corpus Callosum” Syndrome

- Difficulties in learning ("different" children)
- Around puberty: progressive spastic paraparesis
- Slow progressive mental deterioration

Later in life:
- Pseudobulbar signs
- Generalized amyotrophies and weakness

ALS syndrome
Happy joking patients,
(behaving at 35 years as they were 15)

Desperate exhausted parents,
(having fight half of their lives against mental deterioration and facing now disaster)
Thin Corpus Callosum Syndrome (MRI)

A thin CC since the first motor difficulties

Thinner and thinner though the evolution of the disease …
Thin Corpus Callosum Syndrome (MRI)

- Later-stages: involvement of the nearby white matter and subcortical atrophy, mainly in the rostral part of the brain
- Slight cerebellar atrophy
Families in many countries:
- Europe (Italy, Portugal, Germany)
- Brazil
- South Korea
- Australia
- China

Why?
- Because it is frequent?
- Because it is easily recognizable?
  (typical clinic, typical MRI)
1. The first gene to be identified: SPG11
2. Not all the families linked to SPG11 have the TCC phenotype.
3. Inversely, not all the families sharing the TCC phenotype are linked to SPG11
All TCC families have the same phenotype:

- SPG11
- SPG15 (Kjellin syndrome)
- SPG20 (Troyer syndrome)
- SPG21 (Mast syndrome)
TCC phenotype
Frequency of SPG11 and SPG15

- 36 patients with early-onset complex AR-HSP:
  - TCC syndrome: 42%
  - SPG11: 14%
  - SPG15: only 1 patient

  2009 (Schulle)

- 60 non SPG11 patients: SPG15 is the second most frequent

  2009 (Goizet)
AR-spastic paraplegias in Portugal

120 families

Pure late-onset
Miscellanea
With mental retardation
Other TCC
SPG15
SPG11
Pure, early onset
ARSACS
SPG5
SPG32

TCC syndrome
Progress in AR-HSP diagnoses

1994

2011

2020?

Spastic ataxias
ARSACS
SPG32
Miscellanea
Pure, early-onset
With mental retardation

Spastic ataxias
ARSACS
SPG5
SPG32
TCC
Pure late-onset
Comment

- The recessive spastic paraplegias:
  
  - Are becoming more and more complex, but more and more interesting, too.
  
  - And this creates a new hope.
## Differences between dominant and recessive forms

<table>
<thead>
<tr>
<th>Dominant</th>
<th>Recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly pure (92%)</td>
<td>Mostly complex (72.5%)</td>
</tr>
<tr>
<td>But complicated by:</td>
<td></td>
</tr>
<tr>
<td>- urinary retention</td>
<td>- Cognitive defects</td>
</tr>
<tr>
<td>- orthopedic problems:</td>
<td>- Mental retardation</td>
</tr>
<tr>
<td>- pes cavus in early-onset forms</td>
<td>- Dementia</td>
</tr>
<tr>
<td>- chronic low-back pain / sciatic</td>
<td>- Neuropathy</td>
</tr>
<tr>
<td>- knee artrose</td>
<td>- Cerebellar ataxia</td>
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<tr>
<td>- Gain of weight</td>
<td></td>
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</tbody>
</table>
Differences between dominant and recessive forms (in terms of treatment)

**Dominant**
- Good collaboration
- Lifelong physiotherapy
- TT of spasticity
  - Baclofen
  - Intrathecal baclofen bomb
  - Tizanidine
  - Both
  - Botulinum toxin
- TT of bladder complications
- Prevention and TT of orthopaedic complications
- Warm water

**Recessive**
- Deficient collaboration (cognitive defects)
- TT of spasticity limited by
  - early weakness (neuronopathy or neuropathy)
  - difficulties in regulating baclofen bombs
- TT of bladder complications
- Prevention and TT of orthopaedic complications (*pes cavus*)
- Warm water

Genetic counselling: debatable

Genetic counselling: highly recommended