HSP: Clinical highlights and diagnosis

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Norway
Burgos, May 2011
What is HSP?

- Disease?
- Disorder?
- Pathology?
- Diagnosis
- Doctor?
- Treatment?

- State?
- Anomaly?
- Normal variant?
- Not necessary?
- Other?
- Help and support
Hereditær Spastisk Paraparese i Norge

Disputas 11 desember 2009
Anne Kjersti Erichsen
Neurodegenerative disorder

- Indolent onset following normal development, most often in young adults
- Progression with time
- "Symmetrical" symptoms
- Familial occurrence may be difficult to detect (heterogeneity)
- Selective affection of one or several groups of neurones
- Loss of neurons, dendrites, myelin without inflammatory reaction
- As a rule normal lifespan
There are, within recent memory, several examples of diseases that were formally classed as degenerative but are now known to have a metabolic, toxic, or nutritional basis or to be caused by a "slow virus" or a non-viral transmissible agent. It seems reasonable to expect that, with increasing knowledge, more and more diseases whose causes are now unknown will find their way into these categories. Until such time as the causation of all neurorologic diseases is known, there must be a name and a place for a group of diseases that have no known cause are are united only by the common attribute of gradually progressive disintegration of part or parts of the nervous system. In deference to traditional practice, they are collected here under the rubric degenerative diseases.
Neurodegenerative disorder

The adjective degenerative has no great appeal to the modern neurologist. For one thing, it has an unpleasant literary connotation, referring as it does to a state of moral turpitude or deviant behaviour as the consequence of a sociopathic tendency. More important, it is not a satisfactory term medically, since it implies an inexplicable decline from a previous level of normalcy to a lower level of function.....

Rare neurodegenerative disorder

Rare = prevalence < 75/100 000
According to literature 0.1-10 / 100 000
In Norway: ca 7.5/100 000 (min. prevalence)

i.e. ca 400 in Norge
Hereditary rare neurodegenerative disorder

It is evident that many of the diseases included in this category depend on genetic factors, or at least they appear in more than one member of the same family and have been, therefore, more properly designated as **heredodegenerative**.
Diagnosis

• How to make the diagnosis?
  – Symptoms
  – Family history
  – Investigations
Clinical symptoms

- Gait impairment (cannot run)
- Poor balance
- Stiffness
- Muscular weakness in LL
- Cramps, spasms
- Walk on toes
- Urge
Clinical symptoms

• Pure
• Complicated
  – Associated with other neurological symptoms
• Heredity
• Progressive
• Early/late onset

CLINICAL HETEROGENEITY
Other usual complaints

- Depression
- Fatigue (tretthet, utmattelse)
- Anal sphincter problems
- Sexual function problems
- Pain: conspicuously rare, backpain most frequent
- Numbness in feet and legs
Clinical types HSP

"Pure" type
- 1 Gait impairment
- 2 Brisk reflexes
- 3 Muscular weakness in LL
- Usually dominant heredity

"Complex" type
- 1+2+3
- + Other neurological symptoms
- Usually recessive heredity
- Often earlier onset
- Often more severe presentation
Complicated HSP

- Neuropathy
- *Cerebellum affection*
- Muscle atrophy
- *Cognitive impairment* (or mental retardation)
- Parkinsonism-like symptoms, tremor, rigidity, movement disorders
- Psychiatric problems and dementia
- White matter abnormalities
- “Thin CC” (thin corpus callosum)
Findings at examination

• Spasticity
  – Gait
  – rest

• Brisk reflexes
  – LL
  – UL
  – Extensor plantar reflex

• Muscular weakness(+/−)

• Impaired vibration sense
Spasticity

- symptom of damage to nerves pathways or medulla spinalis
- Increased tonus due to lost/decreased control of nerve signals from and to muscles

- leads to stiffness, wrong positions in joints, pain and decreased function, can have a positive effect in case of loss of muscle strength
Muscle strength

- May be diminished at any level
- Patient cannot raise his feet
- Patient cannot raise from supine position
- Patient cannot raise from sitting position
- Patient cannot stand without help/with help
- Running difficult, impossible
- Walking distance
- One cane, crutches, wheeling chair
Spastic Paraplegia Rating Scale (SPRS)

- Walking distance without pause
  - Due to history, walking aids allowed
    - Normal, unlimited
    - Abnormal exhaustion due to spasticity after more than 500m
    - Walking distance less than 500m
    - Walking distance less than 10 m
    - Unable to walk
- Gait quality
  - Patient is asked to walk as fast as possible a 10 meter distance including one turn
    - Normal
    - Mild stiffness, running still possible
    - Clearly spastic gait, interfering with running
    - Spastic gait requiring use of canes/walker
    - Unable to walk for a 10 meter distance even with maximal support
  - Maximum gait speed
  - Climbing stairs
- Speed of stair climbing
- Arising from chair
  - Spasticity -knee flexion
    - (Modified Ashworth scale)
  - Weakness -hip abduction
    - (Medical Research Council 1976)
  - Weakness -foot dorsiflexion
    - (Medical Research Council 1976)
  - Contractures of lower limbs
  - Pain due to SP related symptoms
  - Bladder and bowel function
  - ++++

- Spastic Paraplegia Rating Scale (SPRS)
Investigations

• Mandatory:
  – Radiologic investigation of spine and cerebrum
  – B12

• Eventual:
  – CSF
  – VLCFA
  – Neurography
Markers for HSP??

- Age at onset?
- **Clinical symptoms:**
  - Type of spasticity?
  - Presence and degree of muscle paresis?
  - Associated symptoms
- Biochemical markers?
- Radiological markers?
  - Spectroskopi
  - MR
  - ++

Corpus callosum
AGE OF ONSET

Number of families

Age at onset

- AD pure + complex
- AR pure + complex

ENS 2001 Tallaksen
For all: prognosis = linear progression
## Diagnosis

<table>
<thead>
<tr>
<th>Primary spastic paraparesis</th>
<th>Other primary disease with secondary spastic paraparesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary disorder</td>
<td>Sporadic disorder</td>
</tr>
</tbody>
</table>
"sporadic" vs "hereditary"

• Sporadic often proves hereditary when:
  - small families
  - family history unknown
  - parents died early
  - "wrong" family!
  - de-novo mutations
Diagnosis

• A. Clinical symptoms
  – 1. Progressive spasticity in lower limbs
  – 2. Brisk reflexes
  – 3. Extensor plantar reflexes

• B. Family history
  – 1. Positive
  – 2. None
  – 3. Unknown
Clinical Diagnosis for HSP

• **Definite:**
  – Spasticity in lower limbs
  – Brisk reflexes
  – Extensor plantar reflex
  – Family history

• **Probable**

• **Possible**
<table>
<thead>
<tr>
<th>Definite HSP (certain)</th>
<th>Probable HSP (almost sure)</th>
<th>Possible HSP (cannot be excluded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Other disorders excluded</td>
<td>1. Other disorders excluded+</td>
<td>1. Other disorders excluded</td>
</tr>
<tr>
<td>2. Family history of spastic paraparesis</td>
<td>Two of criteria 2-4</td>
<td>2. Family history of spastic paraparesis</td>
</tr>
<tr>
<td>3. Progressive gait impairment</td>
<td></td>
<td>Symptoms and findings unconclusive</td>
</tr>
<tr>
<td>4. Specific clinical findings</td>
<td></td>
<td>Observation and new examination later</td>
</tr>
</tbody>
</table>
Sporadic: **ASSP** (apparently sporadic spastic paraplegia)

Fink JK. Neurology 2008;71(19):1468-9

- Typically, ASSP is a **transitional diagnosis applied for a number of years until**
  - 1) a pathogenic mutation in an HSP gene is identified or a family history emerges, and the diagnosis is then changed to HSP;
  - 2) the disorder progresses to involve upper extremities, speech, and swallowing, and the diagnosis is then changed to primary lateral sclerosis;
  - 3) another etiology is identified (e.g., amyotrophic lateral sclerosis).
Sporadic

• How many sporadic HSP?
  – 13% of patients in a population based study (19 possibly affected for 127 definite+probable HSP)
  – 30% in a selected population (32 vs 76)
Sporadic

• Which HSP:
  – 5.5% - 6%–12% SPG4 among sporadic cases?
  – 5% SPG3?

• De novo-mutations: unknown frequency
Clinical and genetic findings in a series of Italian children with pure hereditary spastic paraplegia.


- **Aims**: mutational frequency of SPG4, SPG3A, SPG31 and SPG7 genes
- **Material**: 14 Italian children affected by pure HSP (mean age at diagnosis 5.9 years), 13 apparently sporadic
- **Results**:
  - Three SPG4 mutations
  - One novel large deletion in SPG31
  - No mutations in the SPG7 and SPG3A genes
Differential diagnosis

• 80% multiple sclerosis!!
  – Particularly PPMS
Other disorders with spastic paraparesis

- Myelopathy (cervical spinal stenosis etc)
- Rare infections causing myelitis
  - Herpes, Tbc, syphilis
- Rare myelopathies (HTLV1, HIV)
- Vertebrogene/vascular etiology
- Cerebral Paresis
• Vitamin deficiency (B12)
• Other hereditary neurodegenerative disorders (spastic ataxia, FRDA, etc)
• Rare metabolic disorders (ALD, AMN)
• Mitochondrial disorders
• Other non hereditary neurodegenerative disorders
  – PLS
  – ALS
• Paraneoplastic disorders
• Vasculitis
• All these can be diagnosed using blodod tests, radiological examinations, spinal fluid analysis

• But not the following...
Differentiation of Hereditary Spastic Paraparesis From Primary Lateral Sclerosis in Sporadic Adult-Onset Upper Motor Neuron Syndromes

Frans Brugman et al

“In most patients with a sporadic adult-onset upper motor neuron syndrome, differentiation of sporadic presentations of HSP from PLS based on clinical characteristics is unreliable and therefore depends on results of genetic testing.”

Disease progression at least 3 yrs 104 patients

Symptoms

<table>
<thead>
<tr>
<th>SPG4-7(14)</th>
<th>others(90)</th>
</tr>
</thead>
</table>

Leg involvement only (n=52)
1 Leg or both legs only      13

Arm and leg involvement (n=16)
Legs→arms                      1
Legs→right arm               1
Legs→left arm                4
Right leg→right arm→left leg→left arm 1
Right leg→right arm           1
Left leg→left arm             2
Right arm→legs→left arm       1

Legs→arms→bulbar region (13)
Legs→bulbar region→arms      5
Legs→bulbar region           2
Legs→left arm→bulbar region→right arm 1
Left leg→left arm→right leg→right arm 1
leg→right arm→bulbar region  1
Right leg→bulbar region→left leg→arms 1
Right leg→bulbar region      1
Right leg→right arm→left leg→bulbar region 1
Arms→bulbar region→legs      1
Arms→bulbar region          1
Left arm→legs→right arm→bulbar region 1
Bulbar region→arms→legs     2
Bulbar region→left arm      1
Bulbar region→legs→arms     1
Bulbar region→legs           1
Bulbar region→right arm and leg→left arm and leg 1
Bulbar region only          2
Treatment

• NO cure
• Symptomatic
  ❖ Physiotherapy
  ✓ Stretching of the spastic muscles
  ✓ Heat
  ✓ Balance training
  ✓ Swimming pool

❖ Drugs
✓ Antispasmodic
✓ Relaxing, anti anxiety, antidepressive
Treatment

• **Gene therapy??**
  – Not at the moment

• **Alternative therapies?**
  – Acupuncture?
  – Specific types of physiotherapy?
  – Diet?
  – Vitamins?
  – Anti oxydants?
Treatment

• Botulinium toxine
  – For “small” muscles: adductors, ankle muscles
  – Must be tried
  – Maybe best in children?

• Baclofen intrathekal pump
  – For severe spasticity
  – No well established consensus
  – Must be tried, doses needed less than spinal trauma

• Surgery??
Follow up

• Prevent
  – Contractures
  – Pain (spasms, cramps, feilstilling)
  – Bladder problems ++
  – Problems at work
  – Problems at home

• Diagnosis follow up for not yet specified types
• Information about new therapies
• Genetic counselling
Patient with symptoms and findings compatible with HSP.

Exclude diagnoses

Search for genotype

1) Genetic supervision
2) Treatment and follow-up

SPORADIC HSP

IDENTIFIED

OTHER DIAGNOSIS

UNIDENTIFIED

NO FAMILY HISTORY

FAMILY HISTORY
Genetic diagnosis in HSP
From the clinician’s point of view

Chantal ME Tallaksen
Oslo University Hospital
Norway
Burgos, May 2011
Types of heredity

- Sporadic
- Autosomal dominant
- Autosomal recessive
- X-linked
Sporadic
"sporadic" vs "hereditary"

- No known family history
- Disease course as typical HSP
- Thorough investigation reveals no other etiology

- Known cases with similar disease in the family
- Disease course as typical HSP
- No other etiology
"sporadic" vs "hereditary"

- Sporadic often proves hereditary when:
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  - family history unknown
  - parents died early
  - "wrong" family!
  - de-novo mutations
Sporadic: ASSP (apparently sporadic spastic paraplegia)
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• Typically, ASSP is a transitional diagnosis applied for a number of years until 1) a pathogenic mutation in an HSP gene is identified or a family history emerges, and the diagnosis is then changed to HSP; 2) the disorder progresses to involve upper extremities, speech, and swallowing, and the diagnosis is then changed to primary lateral sclerosis; 3) another etiology is identified (e.g., multiple sclerosis).
Autosomal dominant inheritance

- Equally transmitted by men and women
- No skipped generations
- Each child has a 50% chance of inheriting the mutation

- Normal
- Affected
Heredity

AD = autosomal dominant  AR = autosomal recessive

Bakgrunn – HSP i Norge – Artikkel 1 – Artikkel 2 – Artikkel 3 – Artikkel 4 – Oppsummering
X-linked inheritance
Autosomal Recessive Inheritance

Two germ-line mutations (one from each parent) to develop disease
Equally transmitted by men and women

- Noncarrier
- Normal carrier
- Affected carrier
Autosomal recessive inheritance

Pedigree showing autosomal recessive inheritance of sickle cell anaemia
Genetic HSP

- 48 forms described, most only in a few families, many with their own phenotype
- SPG4 = ca 40% of all dominant
- Nr 2 = SPG3 (10-15%), nr 3 = SPG31
- SPG11, 15,21 most frequent recessive forms
- Possibly SPG7??
- 43% genetic diagnosis in our material
GENETIC CLASSIFICATION OF DOMINANT HSP
Dominant HSP

• Most “pure” forms
• But associated signs and symptoms may be present (bladder-sexual dysfunction, orthopedic problems, UL symptoms)
• Some associated neurological symptoms not unfrequent: neuropathy
• Some associated symptoms often mentioned (fatigue, cramps)
<table>
<thead>
<tr>
<th>name</th>
<th>Locus/gene/protein</th>
<th>Onset (yrs)</th>
<th>P/C, occurrence</th>
</tr>
</thead>
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<tr>
<td>SPG3</td>
<td>14q-SPG3A-atlastin</td>
<td>1-7(63)</td>
<td>P-Early onset, many families: <strong>10-15%</strong></td>
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<tr>
<td>SPG4</td>
<td>2p-SPAST-spastin</td>
<td>1-74</td>
<td>P-Most frequent: <strong>50%</strong></td>
</tr>
<tr>
<td>SPG6</td>
<td>15q-<strong>CYPB1</strong></td>
<td>12-35</td>
<td>P-A few families</td>
</tr>
<tr>
<td>SPG8</td>
<td>8q-**KIAA0196-**strumpellin</td>
<td>18-60</td>
<td>P-A few families</td>
</tr>
<tr>
<td>SPG9</td>
<td>10q23.3-q24.1</td>
<td>1-40</td>
<td>C-&lt; 5 families</td>
</tr>
<tr>
<td>SPG10</td>
<td>12q- KIF5A</td>
<td>2-51</td>
<td>P/C-3%</td>
</tr>
<tr>
<td>SPG12</td>
<td>19q-13</td>
<td>1-22</td>
<td>P&lt;-5 families</td>
</tr>
<tr>
<td>SPG13</td>
<td>2q24-<strong>HSP60</strong></td>
<td>17-68</td>
<td>P-1 family</td>
</tr>
<tr>
<td>SPG19</td>
<td>9q33-q34</td>
<td>36-55</td>
<td>P</td>
</tr>
<tr>
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</tr>
<tr>
<td>------------</td>
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<tr>
<td>SPG27</td>
<td>10q22.1-10q24.1</td>
<td>25-45</td>
<td>P-</td>
</tr>
<tr>
<td>SPG29</td>
<td>1p31.1-21.1</td>
<td>11-30</td>
<td>C-?</td>
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<tr>
<td><strong>SPG31</strong></td>
<td>2p- <em>REEP1</em></td>
<td>1-60</td>
<td>P-8%</td>
</tr>
<tr>
<td>SPG33</td>
<td>10q24.2-<em>ZFYVE27</em></td>
<td></td>
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<tr>
<td>SPG36</td>
<td>12q23-24</td>
<td>14-33</td>
<td>C</td>
</tr>
<tr>
<td>SPG37</td>
<td>8p21.1</td>
<td>8-60</td>
<td>P</td>
</tr>
<tr>
<td>SPG38</td>
<td>4p15-p15</td>
<td>12-20</td>
<td>C</td>
</tr>
<tr>
<td>SPG37</td>
<td>8p21.1-1q13.3</td>
<td>8-60</td>
<td>P</td>
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<tr>
<td><strong>SPG42</strong></td>
<td>3q- <em>SLC33A</em></td>
<td>4-42</td>
<td>P-1 family, mild</td>
</tr>
<tr>
<td>SAX1</td>
<td>12p13</td>
<td>10-20</td>
<td>C</td>
</tr>
</tbody>
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### Which type of dominant HSP?

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<td>Most frequent: 50%</td>
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<td>A few families</td>
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</tr>
<tr>
<td>SPG10</td>
<td>12q- KIF5A</td>
<td>2-51</td>
<td>3%</td>
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<tr>
<td>SPG13</td>
<td>2q-HSP60</td>
<td>17-68</td>
<td>1 family</td>
</tr>
<tr>
<td>SPG31</td>
<td>2p- REEP1</td>
<td>1-60</td>
<td>8%</td>
</tr>
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<table>
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<tr>
<th>navn</th>
<th>Locus/gen/protein</th>
<th>Start (år)</th>
<th>Særtrekk/forekomst</th>
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<td>2p- REEP1</td>
<td>1-60</td>
<td>8%</td>
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</tbody>
</table>
Typer dominant HSP, Norge 2010
SPG3
MIM 182600

• Insidious onset, mostly early (<20 yrs)
• Highly variable severity
• Variable progression
• Reduced penetrance
• Reported: scoliosis, axonal neuropathy
## Additional Clinical Features of SPG3A Probands and Affected Family Members


<table>
<thead>
<tr>
<th>Patient</th>
<th>AA Change</th>
<th>Age at Examination, y</th>
<th>Pes Cavus</th>
<th>LL Sensory Problems</th>
<th>UL Sensory Problems</th>
<th>UL Distal Weakness</th>
<th>UL Distal Atrophy</th>
<th>Bladder Disturbances</th>
<th>Additional Features</th>
<th>Severity*</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL-41, II.1</td>
<td>F151S</td>
<td>49</td>
<td>+</td>
<td>Decreased vibration, hyposthesia, hypalgasia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Neuropathy</td>
<td>3</td>
<td>R</td>
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<tr>
<td>SL-53, II.1</td>
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<td>S</td>
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<tr>
<td>SL-53, III.1</td>
<td>L157W</td>
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<td>R</td>
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<tr>
<td>SL-258, III.3</td>
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<td>Decreased vibration</td>
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<td>Neuropathy</td>
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<tr>
<td>SL-121, II.2</td>
<td>R239C</td>
<td>61</td>
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<td>SL-121, III.3</td>
<td>R239C</td>
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<td>HSP-5, III.3</td>
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<td>HSP-5, III.3</td>
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<td>SL-6, II.2</td>
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<td>SL-6, III.3</td>
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<td>SL-239, II.2</td>
<td>Y386H</td>
<td>63</td>
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<td>-</td>
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<td>3</td>
<td>S</td>
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<tr>
<td>SL-239, II.1</td>
<td>Y386H</td>
<td>34</td>
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<td>3</td>
<td>S</td>
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<tr>
<td>SL-166, II.1</td>
<td>M408T</td>
<td>4.5</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Neuropathy, dystartha, bradykinesia, growth retardation</td>
<td>4</td>
<td>R</td>
</tr>
</tbody>
</table>

| SL-109, II.2 | G468A    | 63                    | +         | -                   | -                 | -                 | -                | -                  | Neuropathy         | 1         | S           |
| SL-109, II.3 | G468A    | 40                    | +         | Decreased vibration | -                 | -                 | -                | -                  | -                 | 2         | S           |
| SL-109, II.5 | G468A    | 29                    | +         | -                   | -                 | -                 | -                | -                  | -                 | 2         | S           |
| SL-109, III.1 | G469A    | 10                    | -         | -                   | -                 | -                 | -                | -                  | -                 | 2         | S           |
| HSP-6, II.3 | G482V    | 63                    | -         | -                   | -                 | -                 | -                | -                  | -                 | 0         | NA          |
| HSP-6, II.5 | G482V    | 51                    | -         | -                   | +                 | +                 | -                | -                  | -                 | 2         | S           |
| HSP-6, III.4 | G482V    | 32                    | -         | -                   | -                 | -                 | -                | -                  | -                 | 3         | R           |
| HSP-6, IV.2 | G482V    | 34                    | -         | -                   | -                 | -                 | -                | -                  | [Epilepsy]         | 3         | R           |
| HSP-6, IV.2 | G492W    | 34                    | +         | +                   | -                 | -                 | -                | -                  | -                 | 2         | S           |
| HSP-6, IV.1 | G492W    | 20                    | -         | -                   | -                 | -                 | -                | -                  | -                 | 2         | S           |
| HSP-6, IV.1 | R496W    | 12                    | -         | -                   | -                 | -                 | -                | -                  | -                 | 1         | S           |
| HSP-6, IV.3 | R496W    | 12                    | -         | -                   | -                 | -                 | -                | -                  | -                 | 1         | S           |
| Overall, % | 14        | 15                    | 14        | 20                  | 3                 | 0                 | 17 Complex       | 2-3 (78)           |

Abbreviations: AA, amino acid; LL, lower limbs; NA, not applicable; R, rapid; S, slow; UL, upper limbs; +, present; -, absent; ?, unknown; [epilepsy], brackets indicate not related to hereditary spastic paraplegia.

*Refer to the severity scale in the "Methods" section.

**Results** In 12 probands (6.6%), we identified 12 different SPG3A mutations (11 missense and 1 insertion/frameshift) of which 7 were novel and 3 were de novo. We found **incomplete penetrance in 1 family** (G482V). In most cases, SPG3A mutations were associated with an **early age at onset** (mean, 3 y); however, in 1 family (R495W mutation), symptoms started later (mean, 14 y) with **clear intrafamilial variability** (8-28 y). Six patients with an SPG3A mutation (F151S, Q191R, M408T, G469A, R495W) originating from 5 unrelated families presented with a complex form of hereditary spastic paraplegia associated with a **neuropathy (17%)**. Our electrophysiological and pathological findings confirmed an axonal sensory-motor neuropathy. There was **no correlation between the genotype and the presence of a neuropathy.**
SPG3A is the most frequent cause of hereditary spastic paraplegia with onset before age 10 years

*M. Namekawa et al, NEUROLOGY 2006;66 :112-114*

- *SPG3A* mutations were found in 13.5% (7/52) of AD-HSP families with onset before age 20 years and 31.8% (7/22) in families with onset before age 10 years.
SPG4

- Most frequent, most reported, best known
- “Pure” form
- No phenotype-genotype correlations
- Great intra/inter-familial variability
- Same for men and women
- Faster progression at older onset
- Modifying factors?
How frequent are de novo-mutations?

Penetrance:
- Age-dependent
- Incomplete - ca 85% at 45 yrs
- 20% asymptomatic

NB: therefore difficult to give a precise onset of disease

No anticipation
Spastin mutation identified

- **Affected and symptomatic**
- **Clinically affected but unaware of symptoms**
- **Clinically normal but carrier**
- **Symptomatic but non carrier**
- **Mutation present**

**VARIABLE EXPRESSION AND REDUCED PENETRANCE IN SPG4**

With permission- Alexandra Dürr
Clinical features of 224 SPG4 patients

- Age at onset: 29±17 (0-74) yrs
- Disease duration: 21±15 (0-73) yrs
- Mean age when walking impossible: 48±17 (22-79)
- Severe spasticity at gait/at rest: 34%/19%
- Increased reflexes LL: 91%
- Increased reflexes UL: 27%
- Extensor plantar reflex: 81%
- Proximal muscle weakness LL: 54%
- Distal muscle weakness LL: 36%
- distal muscle wasting: 9%
- Decreased/abolished vibration sense at ankles: 58%/11%
- Urinary urgency / incontinence: 38%/2%
- Pes cavus/scoliosis: 21%/5%
FREQUENCY OF CLINICAL SIGNS IN SPG4
As a function of disease duration

With permission - Alexandra Dürr
Disability, disease duration and age at onset in SPG4

Mean disease duration (years)

Age at onset (years)

Disability stage

<= 35

>35
Additional symptoms

- Cognitive impairment
- Psychiatric disorder
- Cerebellar ataxia
- Dysarthria
- Mental retardation
- Silver phenotype
- Corpus callosum atrophy
- Epilepsy?
- Posterior fossa abnormalities
SPG4: conclusions

- Large inter and intra-heterogeneity
- No sex difference
- Milder form when early onset
- Average onset: young adults (30 yrs)
- No impact on life duration
- Ca 20% affected but asymptomatic (unaware of symptoms)
- Ca 6% clinically asymptomatic
SPG6
MIM 600363

- Few families
- Onset 12-35 yrs
- Insidious onset
- Progressive disorder
- Variable severity
- NIPA1 gene
SPG8
MIM 603563

- Adult onset (18 to 60 years)
- Insidious onset
- Severe phenotype
- Calves atrophy, pes cavus
- Unknown occurrence, few families
- Unpublished own data: not found in 28 AD-HSP index cases, non SPG4- non SPG3
- KIAAO196 gene
- Must be rare
SPG8
MIM 603563

- Unknown occurrence, few families
- Unpublished own data: not found in 28 AD-HSP index cases, non SPG4- non SPG3
- KIAAO196 gene
- Must be rare
SPG10
MIM 604187

- Onset 8-40 yrs
- Few families
- Upper limb weakness may occur later
- Upper limb sensory loss may occur later
- Axonal neuropathy
- Scoliosis
- *KIF5A* gene
SPG10 is a rare cause of spastic paraplegia in European families. 

- CONCLUSIONS: SPG10 accounts for approximately 3% of European autosomal dominant HSP families. All mutations affect the motor domain of kinesin and thus most likely impair axonal transport. Clinically, SPG10 is characterised by spastic paraplegia with mostly subclinical peripheral neuropathy.
SPG31
MIM 610250

• 3-6% in cases with autosomal dominant inheritance.
• Dysphagia (less common)
• Muscle wasting due to chronic denervation
• Amyotrophy
• Distal sensory loss
• Variable severity
• Pure or complicated
SPG42
MIM 612539

• A total of 220 patients with autosomal dominant spastic paraplegia do not display mutations in the SLC33A1 gene (SPG42).

  Schlipf NA et al, Europ Hum Gen 2010

Conclusion:

We consider SLC33A1 gene mutations as being very rare in a European ADHSP cohort, if present at all.
### Which type of dominant HSP?

<table>
<thead>
<tr>
<th>name</th>
<th>Locus/gene/protein</th>
<th>Start (yrs)</th>
<th>Characteristics/occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPG3</td>
<td>14q-SPG3A-atlastin</td>
<td>1-7(63)</td>
<td>Early onset, many families: 10-15%</td>
</tr>
<tr>
<td>SPG4</td>
<td>2p-SPAST-spastin</td>
<td>1-74</td>
<td>Most frequent: 50%</td>
</tr>
<tr>
<td>SPG10</td>
<td>12q- KIF5A</td>
<td>2-51</td>
<td>3%</td>
</tr>
<tr>
<td>SPG31</td>
<td>2p- REEP1</td>
<td>1-60</td>
<td>8%</td>
</tr>
<tr>
<td>name</td>
<td>Locus/gene/protein</td>
<td>onset (yrs)</td>
<td>Characteristics, occurrence</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>SPG1</td>
<td>Xq28- <em>L1CAM</em></td>
<td>1-5</td>
<td><strong>C-</strong> CC agenesis, Mental retardation, Aphasia, Shuffling gait, Adducted thumbs, Hydrocephalus (CRASH). &gt;100 mutations</td>
</tr>
<tr>
<td>SPG2</td>
<td>Xq21- <em>PLP2</em></td>
<td>1-18</td>
<td><strong>C-</strong> From light HSP to Pelizeus Merzbacher phenotype &gt;100 mutations</td>
</tr>
<tr>
<td>SPG16</td>
<td>Xq11.2</td>
<td>1-5</td>
<td><strong>P-</strong> severe. 2 families</td>
</tr>
<tr>
<td>SPG22</td>
<td>Xq13.2- <em>SLC13A2/MCT8</em></td>
<td>1</td>
<td><strong>C-</strong> Mental retardation, dysmorphia, hypotonia, dystonia, low S-thyroxin, Allan-Herndon-Dudley syndrome. Several families.</td>
</tr>
<tr>
<td>SPG34</td>
<td>Xq24-q25</td>
<td>10-25</td>
<td><strong>P-</strong> 1 large Brazilian family</td>
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</table>
HSP - 99 families, 286 individuals
oct. 2010

AR
n= 15

Complex
n=10
Pure
n=5

AD
n=82

Complex
n=9
Pure
N=71

Sporadic
n=71

Complex
n=47
Pure
n=24
Number of individuals: 286
136 men, 130 women
Pure form HSP: 103
Complicated form: 68

<table>
<thead>
<tr>
<th>Heredity</th>
<th>AD</th>
<th>AR</th>
<th>X-linked</th>
<th>sporadic</th>
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<tr>
<td>Antall families</td>
<td>82</td>
<td>15</td>
<td>3</td>
<td>71</td>
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<tr>
<td>Pure/comp</td>
<td>71/9</td>
<td>5/10</td>
<td>3/0</td>
<td>24/47</td>
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</table>
Dominant HSP, Norway 2010
Recessive HSP, Norway 2010
Thank you

- To the HSP-HA research group at Ullevål Universitetssykehus (OUS)
  - Anne Kjersti Erichsen
  - Jeanette Koht
  - Kaja Selmer
  - Sven Olav Løstegaard
  - Iselin Wedding
- To the patients’ association NASPA (www.naspa.no)
- To the dep. of medical genetics at OUS
- To colleagues in all Norway who have helped us.
- To our international partners