SINDROME POST POLIO: PROFILO DIAGNOSTICO e TERAPEUTICO

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The March of Dimes Criteria

1. Prior paralytic poliomyelitis
   with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness, and atrophy
   of muscles on neurological examination, and signs of denervation on electromyography (EMG).

2. A period of partial or complete functional
   recovery
   after acute paralytic poliomyelitis, followed by an interval (usually 15 years or more) of stable neurologic functions.

3. Gradual or sudden onset of progressive and
   persistent muscle weakness or abnormal
   muscle fatigability
   (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain. (Sudden onset
   may follow a period of inactivity, or trauma, or surgery). Less commonly, symptoms attributed to PPS include new
   problems with swallowing or breathing

4. Symptoms persist for at least a year

5. Exclusion of other neurologic, medical, and
   orthopaedic problems as causes of symptoms
PPS

- NEW WEAKNESS
- GENERALIZED FATIGUE
- DECREASED MUSCULAR ENDURANCE
- MUSCLE PAIN
- JOINT PAIN
- COLD INTOLERANCE

Halstead 1985
NEW WEAKNESS
GENERALIZED FATIGUE
DECREASED MUSCULAR ENDURANCE
MUSCLE PAIN
JOINT PAIN
COLD INTOLERANCE
PERIPHERAL NEUROPATHY
JOINT DISEASE
PPS
MYOPATHY
MND
The March of Dimes Criteria

1. **Prior paralytic poliomyelitis**
   with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG).

2. **A period of partial or complete functional recovery**
   after acute paralytic poliomyelitis, followed by an interval (usually 15 years or more) of stable neurologic functions.

3. **Gradual or sudden onset of progressive and persistent muscle weakness or abnormal muscle fatigability**
   (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain. (Sudden onset may follow a period of inactivity, or trauma, or surgery). Less commonly, symptoms attributed to PPS include new problems with swallowing or breathing.

4. **Symptoms persist for at least a year**

5. **Exclusion of other neurologic, medical, and orthopaedic problems as causes of symptoms**
Common symptoms in the general ageing population and could be caused by a considerably
amount of other conditions and illnesses.

Primary goal → rule out other possible contributing factors.
NEUROPHYSIOLOGY
MOTOR CONDUCTION VELOCITY

SENSORY CONDUCTION VELOCITY
LATE RESPONSES
Figure 1: MEPs evoked in biceps and FDI of a normal subject by magnetic stimulation of the motor cortex (upper traces), electrical stimulation over the cervical spine (middle traces) and supramaximal electrical stimulation of musculocutaneous and ulnar nerves (bottom traces). Three individual responses are superimposed on each trace.
Electromyography
(Grimby et al. 1998).

• EMG may show increased amplitude reflecting an enlarged motor unit
• Nerve conduction studies should reveal normal findings for both motor and sensory nerves, except for the parameters regarding the motor units
• Other diagnoses such as peripheral neuropathy and myopathy can be ruled out after neurophysiological examinations.
IMAGING
X-ray
A case of cervical spondylotic amyotrophy resembling post-polio syndrome
Isobe T. et al, 2006
Muscle CT scans

- Computer tomography (CT) scans can be helpful to detect subclinical muscle atrophy
  
  (Ivanyi et al. 1998)

(Kern H et al. Neurorehab Neur Rep 2009)
Muscle MRI

Khoury V. et al, 2008
LABORATORY INVESTIGATIONS
<table>
<thead>
<tr>
<th>Test</th>
<th>Valore</th>
<th>Unità</th>
<th>Riferimento</th>
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<tr>
<td>P-ASOTO UREICO</td>
<td>18,00</td>
<td>mg/dL</td>
<td>(8,00 - 22,00)</td>
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<tr>
<td></td>
<td>6,42</td>
<td>mmol/L urea</td>
<td>(2,85 - 7,85)</td>
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<tr>
<td>P-CREATININA</td>
<td>0,83</td>
<td>mg/dL</td>
<td>(0,60 - 1,30)</td>
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<td></td>
<td>73,3</td>
<td>umol/L</td>
<td>(53,0 - 114,9)</td>
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<td>P-BILIRUBINA TOTALE</td>
<td>0,57</td>
<td>mg/dL</td>
<td>(0,20 - 1,10)</td>
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<tr>
<td></td>
<td>9,7</td>
<td>umol/L</td>
<td>(3,4 - 18,8)</td>
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<tr>
<td>P-CALCIO</td>
<td>9,49</td>
<td>mg/dL</td>
<td>(8,50 - 10,30)</td>
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<tr>
<td></td>
<td>2,37</td>
<td>mmol/L</td>
<td>(2,12 - 2,57)</td>
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<tr>
<td>P-FOSFATI</td>
<td>3,80</td>
<td>* mg/dL</td>
<td>(2,20 - 3,70)</td>
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<tr>
<td></td>
<td>1,22</td>
<td>* mmol/L</td>
<td>(0,71 - 1,19)</td>
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<tr>
<td>P-CLOBO</td>
<td>100</td>
<td>mmol/L</td>
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</tr>
<tr>
<td>P-POTASSIO</td>
<td>3,6</td>
<td>mmol/L</td>
<td>(3,4 - 4,7)</td>
</tr>
<tr>
<td>P-SODIO</td>
<td>141,0</td>
<td>mmol/L</td>
<td>(135,0 - 145,0)</td>
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<tr>
<td>P-URATO</td>
<td>4,7</td>
<td>mg/dL</td>
<td>(2,5 - 7,2)</td>
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<tr>
<td></td>
<td>279,5</td>
<td>umol/L</td>
<td>(148,7 - 428,2)</td>
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<tr>
<td>P-CK</td>
<td>504</td>
<td>U/L</td>
<td>(inf a 50)</td>
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Prior poliomyelitis—IVlg treatment reduces proinflammatory cytokine production

Henrik Gonzalez\textsuperscript{a,b,*}, Mohsen Khadem\textsuperscript{c}, Magnus Andersson\textsuperscript{a,\textsuperscript{c}}, Fredrik Piehl\textsuperscript{c}, Erik Wallström\textsuperscript{a,\textsuperscript{c}}, Kristian Borg\textsuperscript{a,d}, Tomas Olsson\textsuperscript{c}

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\textsuperscript{b} Department of Rehabilitation Medicine, Danderyd Hospital, Stockholm, Sweden
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\textsuperscript{d} Department of Rehabilitation Medicine, Huddinge University Hospital, Stockholm, Sweden

Received 27 October 2003; received in revised form 6 January 2004; accepted 7 January 2004

![Graphs showing cytokine production changes before and after IVlg treatment.](image-url)
Identification of novel candidate protein biomarkers for the post-polio syndrome — Implications for diagnosis, neurodegeneration and neuroinflammation

Henrik Gonzalez\textsuperscript{a,1}, Jan Ottervald\textsuperscript{b,f,s,1}, Kerstin C. Nilsson\textsuperscript{c}, Niclas Sjögren\textsuperscript{d}, Tasso Miliotis\textsuperscript{e}, Helena Von Bahr\textsuperscript{e}, Mohsen Khadem\textsuperscript{f}, Bodil Eriksson\textsuperscript{g}, Sven Kjellström\textsuperscript{h}, Akos Vegvari\textsuperscript{h}, Robert Harris\textsuperscript{f}, György Marko-Varga\textsuperscript{h}, Kristian Borg\textsuperscript{a}, Johan Nilsson\textsuperscript{1}, Thomas Laurell\textsuperscript{i}, Tomas Olsson\textsuperscript{f,1}, Bo Franzén\textsuperscript{b,1}
Post-polio syndrome patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study

E. Farbu\textsuperscript{a,b}, T. Rekand\textsuperscript{a}, E. Vik-Mo\textsuperscript{a}, H. Lygren\textsuperscript{c}, N. E. Gilhus\textsuperscript{b,\textsuperscript{d}} and J. A. Aarli\textsuperscript{a,\textsuperscript{d}}

\textsuperscript{a}Department of Neurology, Haukeland University Hospital, Bergen, Norway; \textsuperscript{b}Neurocenter, Stavanger University Hospital, Stavanger, Norway; \textsuperscript{c}Department of Physiotherapy, Haukeland University Hospital, Bergen, Norway; and \textsuperscript{d}Institute of Clinical Medicine, University of Bergen, Bergen, Norway

\textit{European Journal of Neurology 2007, 14: 60–65}

<table>
<thead>
<tr>
<th></th>
<th>IvIg (mean)</th>
<th>Placebo (mean)</th>
<th>95% CI for the difference</th>
<th>(P)-value</th>
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<td><strong>TNF-(\alpha), CSF (pg/ml)</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>1.37</td>
<td>1.97</td>
<td>-0.41 to 1.62</td>
<td>&gt; 0.05</td>
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<tr>
<td>1 month</td>
<td>1.10</td>
<td>2.13</td>
<td>0.13 to 1.92</td>
<td>0.028</td>
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<td><strong>TNF-(\alpha), serum (pg/ml)</strong></td>
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<tr>
<td>Baseline</td>
<td>1.82</td>
<td>2.24</td>
<td>-1.11 to 1.95</td>
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<td>1 month</td>
<td>1.93</td>
<td>2.11</td>
<td>-1.36 to 1.71</td>
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<td><strong>IL-6, CSF. (pg/ml)</strong></td>
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<tr>
<td>Baseline</td>
<td>1.74</td>
<td>1.41</td>
<td>-1.22 to 0.55</td>
<td>&gt; 0.05</td>
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<td>1 month</td>
<td>2.33</td>
<td>1.68</td>
<td>-2.1 to 0.79</td>
<td>&gt; 0.05</td>
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Post-polio syndrome: clinical manifestations and cerebrospinal fluid markers

Michele Fiorini,
Gianluigi Zanusso,
Andreatta Baj,
Laura Bertolasi,
Antonio Toniolo &
Salvatore Monaco

Table 2. Reports of cerebrospinal fluid 14-3-3 protein assay in different neurological disorders.

<table>
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<tr>
<th>Disorder</th>
<th>Positive/negative 14-3-3 assay</th>
<th>Ref.</th>
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<td>Viral meningencephalitis</td>
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<td>68</td>
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<tr>
<td></td>
<td>12/24</td>
<td>69</td>
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<tr>
<td>Nonviral meningencephalitis</td>
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<tr>
<td></td>
<td>12/20</td>
<td>70</td>
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<tr>
<td>Multiple sclerosis</td>
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<td>68</td>
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<td></td>
<td>0/8</td>
<td>69</td>
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<td></td>
<td>5/38</td>
<td>71</td>
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<td></td>
<td>3/37</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>25/111 (ELISA)</td>
<td>73</td>
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<tr>
<td></td>
<td>24/63</td>
<td>74</td>
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<tr>
<td></td>
<td>14/16</td>
<td>75</td>
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<td>Alzheimer disease</td>
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<td>69</td>
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<tr>
<td></td>
<td>4/20</td>
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<td>Other dementias</td>
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<td>68</td>
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<td></td>
<td>0/14</td>
<td>69</td>
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<tr>
<td></td>
<td>4/31</td>
<td>76</td>
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<tr>
<td>Stroke</td>
<td>4/8</td>
<td>69</td>
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<tr>
<td>Paraneoplastic diseases</td>
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<td>Guillain–Barre syndrome</td>
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<td>68</td>
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<tr>
<td></td>
<td>29/38</td>
<td>78</td>
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<tr>
<td>Motor neuron disease</td>
<td>0/7</td>
<td>68</td>
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<tr>
<td>Noninflammatory neuropathy</td>
<td>0/16 (ELISA)</td>
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Postpolio Syndrome and CSF Markers

Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>CSF protein level (mg/dl)</th>
<th>Oligodonal Bands</th>
<th>Tau (pg/ml)</th>
<th>1D PAGE 14-3-3</th>
<th>2D PAGE high molecular weight 14-3-3</th>
<th>Cystatin C*</th>
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<tr>
<td>1</td>
<td>Post-polio</td>
<td>52</td>
<td>0.24</td>
<td>nd</td>
<td>374</td>
<td>±</td>
<td>+</td>
<td>0.16</td>
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<td>2</td>
<td>Post-polio</td>
<td>73</td>
<td>0.85</td>
<td>nd</td>
<td>115</td>
<td>±</td>
<td>+</td>
<td>0.98</td>
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<tr>
<td>3</td>
<td>Post-polio</td>
<td>50</td>
<td>0.41</td>
<td>nd</td>
<td>&lt;60</td>
<td>±</td>
<td>+</td>
<td>0.22</td>
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<tr>
<td>4</td>
<td>Post-polio</td>
<td>58</td>
<td>0.87</td>
<td>nd</td>
<td>199</td>
<td>+</td>
<td>+</td>
<td>4.66</td>
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<tr>
<td>5</td>
<td>Post-polio</td>
<td>81</td>
<td>0.66</td>
<td>nd</td>
<td>210</td>
<td>+</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>Post-polio</td>
<td>57</td>
<td>0.25</td>
<td>nd</td>
<td>&lt;60</td>
<td>±</td>
<td>+</td>
<td>nd</td>
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<tr>
<td>7</td>
<td>Post-polio</td>
<td>52</td>
<td>0.35</td>
<td>nd</td>
<td>196</td>
<td>±</td>
<td>+</td>
<td>1.37</td>
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<tr>
<td>8</td>
<td>Post-polio</td>
<td>66</td>
<td>0.37</td>
<td>+</td>
<td>174</td>
<td>-</td>
<td>+</td>
<td>0.91</td>
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<tr>
<td>9</td>
<td>Post-polio</td>
<td>65</td>
<td>0.37</td>
<td>nd</td>
<td>167</td>
<td>±</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>Post-polio</td>
<td>51</td>
<td>0.37</td>
<td>nd</td>
<td>195</td>
<td>±</td>
<td>+</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td>Post-polio</td>
<td>51</td>
<td>0.24</td>
<td>nd</td>
<td>198</td>
<td>-</td>
<td>+</td>
<td>nd</td>
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<td>12</td>
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<td>73</td>
<td>0.25</td>
<td>nd</td>
<td>160</td>
<td>±</td>
<td>+</td>
<td>0.32</td>
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<td>13</td>
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<td>75</td>
<td>0.15</td>
<td>nd</td>
<td>401</td>
<td>±</td>
<td>+</td>
<td>0.56</td>
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<tr>
<td>14</td>
<td>Post-polio</td>
<td>60</td>
<td>0.21</td>
<td>nd</td>
<td>63</td>
<td>±</td>
<td>+</td>
<td>0.36</td>
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<tr>
<td>15</td>
<td>Polio</td>
<td>54</td>
<td>0.20</td>
<td>+</td>
<td>&lt;60</td>
<td>+</td>
<td>+</td>
<td>0.19</td>
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<td>16</td>
<td>Post-polio</td>
<td>54</td>
<td>0.27</td>
<td>nd</td>
<td>86</td>
<td>nd</td>
<td>+</td>
<td>1.99</td>
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<td>nd</td>
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<td>+</td>
<td>7.5</td>
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<td>18</td>
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<td>nd</td>
<td>345</td>
<td>nd</td>
<td>+</td>
<td>11.77</td>
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<tr>
<td>19</td>
<td>Polio</td>
<td>62</td>
<td>0.30</td>
<td>nd</td>
<td>390</td>
<td>+</td>
<td>+</td>
<td>0.15</td>
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</tbody>
</table>

CSF Analysis

![Image of CSF Analysis](image-url)
A, D: PPS; C: stable polio; F: GBS; D: ALS
Distinct 14-3-3 isoforms were identified with specific antibodies and are depicted with colors.
Conclusions: CSF Markers in PPS

- 14-3-3 protein levels are increased in the CSF of patients affected with PPS. This finding is more evident by 2D-PAGE analysis likely related to the presence of dimeric forms of 14-3-3 protein.

- 2D-PAGE analysis of 14-3-3 protein shows a pattern similar to that observed in neurological inflammatory disorders but different from ALS.

- To provide insights about the inflammatory events occurring in PPS a detailed characterization of distinct 14-3-3 protein isoforms is ongoing.

- However, the low Tau protein levels detected in PPS exclude an acute or widespread neuronal damage.
Clinical picture

- Asymmetrical and often scattered weakness, involving several segments of the spinal cord,
- No signs of upper motor neuron involvement
- No rapid and severe progressive deterioration.
- Tendon reflexes are often weakened or absent in the same scattered pattern.
- Fasciculations can be observed in the affected muscles, but is not generalized.
- Post-exercise fatigue and decreased muscular endurance during activity
- Muscle pain
History

• Raymond (1875): first case report on new muscle weakness several years after paralytic poliomyelitis (polio). A 19-year old tanner who suffered from new atrophy in his shoulder more than a decade after having passed acute polio for Charcot.

• Polio was considered to be a three-phasic illness starting with acute paralysis, followed by a recovery and subsequently a stable phase with more or less residual weakness.

• This dogma changed as the large numbers of polio survivors in the 20th century grew older and reported new symptoms several decades after the acute illness and data were systematically recorded.
• Halstead (1985): POST-POLIO as a new term to cover all aspects of late consequences occurring several years after acute paralytic polio. The symptoms included were new weakness, generalized fatigue, decreased muscular endurance, muscle pain, joint pain, and cold intolerance.

• Halstead and Dalakas: suggestive criteria and definition

1. Confirmed history of polio
2. Partial or fairly complete neurological and functional recovery after the acute episode
3. Period of at least 15 years with neurological and functional stability
4. Two or more of the following health problems occurring after a stable period: extensive fatigue, muscle and/or joint pain, new weakness in muscles previously affected or unaffected, new muscle atrophy, functional loss, cold intolerance
5. No other medical explanation found
6. Gradual or abrupt onset of new neurogenic weakness
• PPS is a condition following paralytic polio in which the muscle strength and clinical function are slowly deteriorating, without any dramatic loss of muscle strength as in motor neuron diseases.

• Guidelines for diagnosis and management
  - US (MoD) (March of Dimes 2000)
  - Europe (EFNS) (Farbu et al. 2006)
• Very subtle and insidious start.
• Clinical course rather modest, with no devastating progressive weakness (such as in ALS).
• Once the threshold for the neuromuscular compensatory mechanisms is passed, a more stepwise deterioration can be seen.

• Overuse and metabolic stress on enlarged motor units, deterioration of the neuromuscular junction, the normal ageing process and inflammatory changes are thought to contribute to the clinical picture.
• Muscle weakness, atrophy, generalised fatigue, post-exercise fatigue, muscle pain, fasciculations, cramps, cold intolerance, and joint pain dominate.

• Common symptoms in the general ageing population and could be caused by a considerably amount of other conditions and illnesses.

• Primary goal → rule out other possible contributing factors.
The March of Dimes Criteria

- Prior paralytic poliomyelitis with evidence of motor neuron loss, as confirmed by history of the acute paralytic illness, signs of residual weakness, and atrophy of muscles on neurological examination, and signs of denervation on electromyography (EMG).

- A period of partial or complete functional recovery after acute paralytic poliomyelitis, followed by an interval (usually 15 years of more) of stable neurologic function.

- Gradual or sudden onset of progressive and persistent muscle weakness or abnormal muscle fatigability (decreased endurance), with or without generalized fatigue, muscle atrophy, or muscle and joint pain. (Sudden onset may follow a period of inactivity, or trauma, or surgery). Less commonly, symptoms attributed to PPS include new problems with swallowing or breathing.

- Symptoms persist for at least a year.

- Exclusion of other neurologic, medical, and orthopaedic problems as causes of symptoms.
Prior poliomyelitis—IVlg treatment reduces proinflammatory cytokine production

Henrik Gonzalez, Mohsen Khademi, Magnus Andersson, Fredrik Piehl, Erik Wallström, Kristian Borg, Tomas Olsson

Journal of Neuroimmunology 150 (2004) 139–144

CSF

After IVlg treatment
Interpretation

- Kallikrein 6: normally expressed in neurons and oligodendrocytes up-regulated after inflammatory damages. (Expression of neurite outgrowth or toxic to oligodendrocytes)

- Fragments of Gelsolin: Related to an increase of caspase 3 activity and reduction of antiapoptotic effect

- Hemopexin: Expressed in acute phases of CNS damage

Expression of a chronic inflammatory CNS damage, possibly related to an autoimmune mechanism or a viral persistence ??????

- These proteins play a role in the pathophysiology

- Candidate Biomarkers
Standard CSF in Post-Polio Syndrome

CSF Standard

- Suspected PPS

Exclusion of other Diagnoses

Protein ↑ / =
- Detection of Oligoclonal bands
- Detection of Mononuclear cells

Poliovirus Genomic Sequences
The three poliovirus serotypes (PVs) cause acute paralytic poliomyelitis. Decades after being hit by polio, survivors may develop a condition known as post-polio syndrome (PPS). PPS is characterized by extreme fatigue, progressing muscular weakness and chronic pain. The pathogenesis is unclear and, thus, empirical therapies are employed. PVs are known to be able to persist in infected host cells both in vitro and in vivo. The understanding of PV genomes has made it possible to set up sensitive and specific molecular tests capable of detecting minute amounts of virus in samples from PPS patients. Current data indicate that complete PV genomes (or genomic fragments) remain present, decades after acute paralysis, in the CNS of these patients. Virus persistence is hypothesized to bring about chronic inflammation, immune-mediated injury and decreased expression of neurotrophic factors. Establishing a pathogenetic link between PV persistence and PPS would be extremely relevant to the development of an etiologic therapy aimed at virus eradication.

**Post-polio syndrome**
The three poliovirus serotypes (PVs) cause acute paralysis. Poliovirus RNA (-740 nucleotides) has a complex secondary structure representing the internal ribosome entry site (IRES). It is a highly conserved region of the 3′-terminal untranslated region of the genomic RNA.
Hypothesized Mechanisms leading to Motorneuron Dysfunction

Persistence of Poliovirus

Deregulation of Inflammatory and Immune response

Alteration of regulatory mechanisms of enlarged motor units

Degenerative process

Reinnervation Giant Motor Units

Stable Polio

Dysfunction of enlarged Motor Units

Early Disease

Late Disease

Postpolio Syndrome

CSF ?

Neuronal Damage
PATHOGENESIS

HYPOTHESIS

VIRAL

DEGENERATIVE

INFLAMMATORY
Post-polio syndrome: clinical manifestations and cerebrospinal fluid markers

Michele Fiorini, Gianluigi Zanusso, Andreina Baj, Laura Bertolasi, Antonio Toniolo, Salvatore Monaco


14-3-3
Tau
Cystatina C
<table>
<thead>
<tr>
<th>Intravenous immunoglobulin</th>
<th>Ig vena</th>
<th>30 g/die per 3 giorni</th>
<th>16 pz</th>
<th>INF-(\gamma) mRNA, TNF-(\alpha) liquor e sangue</th>
<th>6/8 sett</th>
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<tr>
<td>In postpolio syndrome</td>
<td>Ig vena</td>
<td>30 g/die per 3 giorni</td>
<td>14 pz</td>
<td>qualità della vita (=forza e performance fisica)</td>
<td>2 mesi</td>
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<td>Farbu et al</td>
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<td>forza muscolare</td>
<td>2/3 mesi</td>
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<tr>
<td>Intravenous immunoglobulin</td>
<td>Ig vena</td>
<td>400mg/Kg per 5 giorni</td>
<td>1 pz</td>
<td>forza muscolare</td>
<td>2 mesi</td>
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<td>for post-polio syndrome:</td>
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<td>a randomised controlled trial</td>
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<td>Amdal, O. et al.</td>
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<td>Lancet Neurol. 2006; 5:493-500</td>
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<tr>
<td>Post-polio syndrome patients treated with intravenous immunoglobulin: a double-blinded randomized controlled pilot study</td>
<td>Ig vena</td>
<td>2g/Kg (in 2-4 giorni)</td>
<td>20 pz</td>
<td>VAS</td>
<td>2/3 mesi</td>
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<tr>
<td>E. Farbu(^2), T. Rekasi(^3), E. Váci(^2), H. Lugner(^1), N. E. Gihul(^2) and J. A. Aagi(^2)</td>
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<td>European Journal of Neurology 2007, 14: 60-66</td>
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</table>
• The secondary outcome measures were:
• 1. muscle strength;
• 2. muscle endurance;
• 3. fatigue;
• 4. pain;
• 5. adverse events subdivided into minor adverse events and serious adverse events (resulting in cessation of treatment, requiring hospitalisation or being life-threatening or fatal).
“IMMUNOGLOBULIN TREATMENT IN POSTPOLIO SYNDROME”
Two arms double blind RCT (treatment vs placebo)
INCLUSION CRITERIA

1. Postpolio diagnosis according to Halstead’s criteria (Orthopedics 1991; 14: 1209-1217), reconfirmed in 2006 by ENFS
   - anamnesis and neurological examination
   - electrophysiological examination

2. Exclusion of any other neurological, orthopaedic or medical problems as causes of symptoms
   - electrophysiological examination
   - laboratory analysis
   - (orthopaedic examination)
   - (imaging)
## Diagnosis of postpolio syndrome

1. History of previous established episodes of paralytic polio
2. Partial or fairly complete recovery
3. Period of functional and clinical stability of at least 15 years
4. Sudden or gradual onset of new symptoms and signs of muscle dysfunction:
   - muscle weakness
   - new muscle atrophy
   - muscle or joint pain,
   - loss of muscle function
   - cold intolerance
Electrophysiological examination:

ENG and EMG

- Signs of “ancient” neurogenic reorganization due to previous poliovirus infection
- Signs of new lower motor neuron lesions $\rightarrow$ reactivation of pathogenic pathway

PESS

- Normal sensory findings; useful to rule out root or nerve trunk pathology
Further investigations:

**Imaging studies:** mainly Back bone MRI in order to rule out entrapment or root compression

**ORTHOPEDIC EVALUATION:** to rule out bone or joint involvement

Exclusion of patients with POST-POLIO SYNDROME and contemporary RADICULOPATHY in the same innervation territories → **SELECTED POPULATION**
EXCLUSION CRITERIA

- BMI > 30
- Diabetes Mellitus
- Mild or severe heart disease
- Renal Failure
- Hypertension
- History of thromboembolism
- Oral anticoagulant therapy
- Previous IVIG treatment
- IgA deficiency
- Other autoimmune diseases
- Age > 70yrs
- Other causes of controindication ti therapy
- Other causes able to explain the complained symptoms
TREATMENT

- Immunoglobuline e.v. alla dose di 0,4 g/Kg/daily or Placebo (saline) for 5 days
- Direct monitoring by a clinic or a paraclinic involved in the project
1. Selection of patients according to inclusion and exclusion criteria
2. Presentation of the project to the patient which also receives informed consent form
3. Electrophysiological examination:
   - 4 limbs ENG
   - EMG $\rightarrow$ stable muscle (no variations in the time)
     $\rightarrow$ healthy muscle (not interested by acute infection)
     $\rightarrow$ worsened muscle (new muscle weakness after a period of clinical stability of at least 15 years)
   - 4 limbs TMS
   - 4 limbs SEP
4. Laboratory workup:
   - Blood count
   - IgA titration
   - Haepatic and renal function
   - Serology for HIV and haepatitis
<table>
<thead>
<tr>
<th>Section</th>
<th>Measurement</th>
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<tbody>
<tr>
<td>Muscular Strength</td>
<td>MRC Dynamic dynamometer</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue severity scale (FSS)</td>
</tr>
<tr>
<td>Pain</td>
<td>Analogue Scale (VAS) 101 Point Numerical Rating (101-PNR)</td>
</tr>
<tr>
<td>Quality of life</td>
<td>SF-36 (36 item Short-Form)</td>
</tr>
<tr>
<td>Muscle function</td>
<td>6 minutes walking test (6 MWT)</td>
</tr>
</tbody>
</table>
**PHASE III**

**TREATMENT**

**25 PAZIENTS**
IVIG 0.4 g/Kg/daily for 5 consecutive days

**25 CONTROLLI**
PLACEBO (saline) at the same way

Infusion:
- initial speed: 0.46-0.92 ml/kg/h $\rightarrow$ 10-20 gtt/min
- maximal speed: 1.85 ml/Kg/h $\rightarrow$ 40 gtt/min
## PHASE IV

### CLINICAL FOLLOW-UP

With:
- MRC and Dynamometer
- FSS
- VAS and 101-PNR
- SF-36
- 6 MWT

### ELECTROPHYSIOLOGICAL FOLLOW-UP

Mediante:
- 4 limbs ENG
- 3 muscle EMG
- 4 limbs SEP
- 4 limbs TMS

| 2 months | 4 months |
Estimated period of participation of the patient: 6 months

The patient can stop the treatment and leave the study anytime.
• Double blind study
• Randomization codes elaborated with statistical software STATA 9.2 (HYPERLINK) by the department of epidemiology and medical statistics, of the University of Verona and delivered to Bussolengo’s ASL pharmacist
• Every patient gets a code which he keeps for the duration of the whole study
• Pharmacy of Bussolengo’s Hospital prepares the samples: same bags labelled and screened containing venous Ig and saline
MAIN RESPONSE VARIABLES

• PRIMARY END POINT:
  better score of physical component of SF-36 in treated subjects compared with placebo

• SECONDARY END POINT:
  – Increase in muscular strength (MRC, Dynamometer)
  – Reduction of fatigue (FSS)
  – Reduction of pain (VAS, 101-PNR)
  – Improvement in muscle function (6 MWT)
Assuming:
• An improvement of at least 4 points in the score of physical component of SF-36 (Gonzales et al. 2004; Kaponides et al. 2006)
• Alfa= 0,05
• 80% power
• correlazione tra due misurazioni sullo stesso soggetto di 0,9
• rapporto di randomizzazione 1:1

...we need 21 subjects in every arm

Which will be raised to **25 SUBJECTS** in account of eventual dropouts
“INTENTION TO TREAT” analysis
Primary and secondary endpoints:
Comparison of differences in the score of the scale used before and after treatment in the two groups by means of
- T-TEST (in case of gaussian distribution)
- TEST of MANN-WHITNEY (in case of non gaussian distribution)

If necessary check out for biases (eg, severity of pathology, age):
- COVARIANCE ANALYSIS
  - Dependent variable: difference between values in variables before and after treatment/placebo
  - Independent variable: group (treatment/placebo); age; disease severity

Statistical analysis by means of software STATA 9.2
SF36- pc

Wilcoxon  p=0.02

IgV

placebo

T0
T1
FSS

Graph showing FSS scores over time (T0, T1, T2) with placebo and IgV conditions.
<table>
<thead>
<tr>
<th>STRATIFIED ANALYSIS</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>M</td>
</tr>
<tr>
<td><strong>Age of infection</strong></td>
</tr>
<tr>
<td>&lt;15,5</td>
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<tr>
<td>&gt;15,5</td>
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<tr>
<td><strong>Age of worsening</strong></td>
</tr>
<tr>
<td>&lt;50</td>
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<tr>
<td>&gt;50</td>
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<tr>
<td><strong>tempo X trattamento</strong></td>
</tr>
<tr>
<td>&lt;7,5</td>
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<tr>
<td>&gt;7,5</td>
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<tr>
<td><strong>FSS T0</strong></td>
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<tr>
<td>&lt;53,5</td>
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<tr>
<td>&gt;53,5</td>
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<tr>
<td><strong>VAS T0</strong></td>
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<tr>
<td>&lt;5,5</td>
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<tr>
<td>&gt;5,5</td>
</tr>
<tr>
<td><strong>6 min walking T0</strong></td>
</tr>
<tr>
<td>&lt;296,5</td>
</tr>
<tr>
<td>&gt;296,5</td>
</tr>
<tr>
<td><strong>SF36-pcT0</strong></td>
</tr>
<tr>
<td>&lt;24,9</td>
</tr>
<tr>
<td>&gt;24,9</td>
</tr>
</tbody>
</table>
Sex

6 min WALKING

IgV  placebo

T test p=0.009  Wilcoxon  p=0.012

m

men  women  men  women

T0  T1
Sex

6 min WALKING

Wilcoxon p=0.012

placebo

T0

T1
IgV placebo

**Age of infection**

**FSS**

Wilcoxon p=0.008
**Time to treatment**

![Graph showing FSS with IgV and placebo groups](attachment:image.png)

- **IgV**
  - Wilcoxon $p=0.012$

- **Placebo**
  - *Significance Marker*

**Time Groups**:
- <7.5 yrs
- >7.5 yrs

**Comparison**:
- T0
- T1

**Legend**:
- T0
- T1
Wilcoxon p=0.002
6 min Walking

IgV placebo

Wilcoxon p=0.04

FSS T0

Serie 1

Serie 2

<53.5 <53.5 >53.5

* >53.5

T0 T1
6 min walking

FSS

IgV placebo

Wilcoxon p=0.02

Serie1 Serie2

<296.5 <296.5 >296.5 >296.5

T0 T1
• Primary end point: Ig treatment was significantly effective

• Compared with males, females have a different response to treatment
• a late acute infection determines a best therapeutical response

• when treatment is administered after a few years since the beginning of symptoms it seems to be more effective
CONCLUSION

• most severe clinical condition receive the greatest benefit from the treatment
A randomized controlled trial of IV immunoglobulin in patients with postpolio syndrome

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d Department of Public Health and Medicine, Unit of Epidemiology and Medical Statistics, University of Verona, Italy
e Rehabilitation Medicine, National Centre for Polio Survivors, Malcesine Hospital, Malcesine, Italy

Classification of evidence: Class I evidence indicates that IV Ig did not change SF-36 PCS, and Class II evidence indicates that IV Ig improved scores on the SF-36 MCS, RP, and RE.