POST POLIO SYNDROME: DIAGNOSTIC TOOLS

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Rehabilitation Medicine, National Centre for polio survivors, Hospital of Malcesine, Italy
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

PPS

MND

PERIPHERAL NEUROPATHY

MYOPATHY

JOINT DISEASE
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).

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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 $\rightarrow$ rule out other possible contributing factors.
NEUROPHYSIOLOGY
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.
IMAGING
X-ray
A case of cervical spondylotic amyotrophy resembling post-polio syndrome
Isobe T. et al, 2006
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>Norma</th>
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<tbody>
<tr>
<td>P-AZOTO UREICO</td>
<td>18,00</td>
<td>mg/dL</td>
<td>(8,00 - 22,00)</td>
</tr>
<tr>
<td></td>
<td>6,42</td>
<td>mmol/L</td>
<td>(2,85 - 7,85)</td>
</tr>
<tr>
<td>P-CREATININA</td>
<td>0,83</td>
<td>mg/dL</td>
<td>(0,60 - 1,30)</td>
</tr>
<tr>
<td></td>
<td>73,3</td>
<td>umol/L</td>
<td>(53,0 - 114,9)</td>
</tr>
<tr>
<td>P-BILIRUBINA TOTALE</td>
<td>0,57</td>
<td>mg/dL</td>
<td>(0,20 - 1,10)</td>
</tr>
<tr>
<td></td>
<td>9,7</td>
<td>umol/L</td>
<td>(3,4 - 18,8)</td>
</tr>
<tr>
<td>P-Calcio</td>
<td>9,49</td>
<td>mg/dL</td>
<td>(8,50 - 10,30)</td>
</tr>
<tr>
<td></td>
<td>2,37</td>
<td>mmol/L</td>
<td>(2,12 - 2,57)</td>
</tr>
<tr>
<td>P-FOSFATI</td>
<td>3,80</td>
<td>* mg/dL</td>
<td>(2,20 - 3,70)</td>
</tr>
<tr>
<td></td>
<td>1,22</td>
<td>* mmol/L</td>
<td>(0,71 - 1,19)</td>
</tr>
<tr>
<td>P-CLORO</td>
<td>100</td>
<td>mmol/L</td>
<td>(98 - 107)</td>
</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>
</tr>
<tr>
<td>P-URATO</td>
<td>4,7</td>
<td>mg/dL</td>
<td>(2,5 - 7,2)</td>
</tr>
<tr>
<td></td>
<td>279,5</td>
<td>umol/L</td>
<td>(148,7 - 428,2)</td>
</tr>
<tr>
<td>P-CK</td>
<td>504</td>
<td>U/L</td>
<td>(inf a 50)</td>
</tr>
</tbody>
</table>
Prior poliomyelitis—IvIg treatment reduces proinflammatory cytokine production

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

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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 Khademi\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{i}, 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{a,d} and J. A. Aarli\textsuperscript{a,d}

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European Journal of Neurology 2007, 14: 60–65

Table 3 TNF-\( \alpha \), and IL-6 before and after treatment of post polio syndrome (PPS) patients.

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

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Gianluigi Zanusso,
Andreina Baj,
Laura Bertolasi,
Antonio Toniolo &
Salvatore Monaco†
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Table 2. Reports of cerebrospinal fluid 14-3-3 protein assay in different neurological disorders.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Positive/negative 14-3-3 assay</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Viral meningoencephalitis</td>
<td>2/7</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>12/24</td>
<td>[69]</td>
</tr>
<tr>
<td>Nonviral meningoencephalitis</td>
<td>2/11</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>12/20</td>
<td>[70]</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1/10</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>0/8</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td>5/38</td>
<td>[71]</td>
</tr>
<tr>
<td></td>
<td>3/37</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>25/1114 (EUSA)</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td>24/63</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td>14/16</td>
<td>[75]</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>1/49</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td>4/20</td>
<td>[76]</td>
</tr>
<tr>
<td>Other dementias</td>
<td>0/5</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>0/14</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td>4/31</td>
<td>[76]</td>
</tr>
<tr>
<td>Stroke</td>
<td>4/8</td>
<td>[69]</td>
</tr>
<tr>
<td>Paraneoplastic diseases</td>
<td>10/70</td>
<td>[77]</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>0/5</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>29/38</td>
<td>[78]</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>0/7</td>
<td>[68]</td>
</tr>
<tr>
<td>Noninflammatory neuropathy</td>
<td>0/16 (EUSA)</td>
<td>[73]</td>
</tr>
</tbody>
</table>

Postpolio Syndrome and CSF Markers

Patients

Table 3. Demographic, clinical and laboratory features of patients.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>CSF protein level (mg/dl)</th>
<th>Oligoclonal 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>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>7</td>
<td>Post-polio</td>
<td>52</td>
<td>0.35</td>
<td>nd</td>
<td>198</td>
<td>±</td>
<td>+</td>
<td>1.37</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>12</td>
<td>Post-polio</td>
<td>73</td>
<td>0.25</td>
<td>nd</td>
<td>160</td>
<td>±</td>
<td>+</td>
<td>0.32</td>
</tr>
<tr>
<td>13</td>
<td>Polio</td>
<td>75</td>
<td>0.15</td>
<td>nd</td>
<td>401</td>
<td>±</td>
<td>+</td>
<td>0.56</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>17</td>
<td>Post-polio</td>
<td>52</td>
<td>0.24</td>
<td>nd</td>
<td>331</td>
<td>nd</td>
<td>+</td>
<td>7.5</td>
</tr>
<tr>
<td>18</td>
<td>Post-polio</td>
<td>62</td>
<td>0.22</td>
<td>nd</td>
<td>345</td>
<td>nd</td>
<td>+</td>
<td>11.77</td>
</tr>
<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>
</tr>
</tbody>
</table>
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.
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.
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
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Prior poliomyelitis—IvIg treatment reduces proinflammatory cytokine production

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

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CSF

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

- 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
Hypothesized Mechanisms leading to Motorneuron Dysfunction

Persistence of Poliovirus

Degenerative process

Deregulation of Inflammatory and Immune response

Alteration of regulatory mechanisms of enlarged motor units

Reinnervation

Giant Motor Units

Stable Polio

Early Disease

Late Disease

Postpolio Syndrome

Neuronal Damage

CSF?
Distinct 14-3-3 isoforms were identified with specific antibodies and are depicted with colors.