Post-polio syndrome: clinical manifestations and cerebrospinal fluid markers

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Post-polio syndrome (PPS) refers to a constellation of new neurological, musculoskeletal and general symptoms occurring in survivors of poliomyelitis decades after acute paralytic and nonparalytic disease. The common manifestations of PPS include generalized, central and peripheral fatigue, muscle weakness and musculoskeletal pain. The pathogenesis of PPS remains obscure. Three prevailing hypotheses have been advanced: stress-induced degeneration of surviving neurons, persistent poliovirus replication or virus reactivation and immune-mediated damage. The diagnosis of PPS is based on medical history and clinical examination, since no specific diagnostic tests are available. In the light of recent studies demonstrating a partial beneficial effect of intravenous immunoglobulin, this article will focus on cerebrospinal fluid biomarkers reflecting disease activity and pathogenic processes in PPS.

Keywords: 14-3-3 proteins, antivirals, cystatin C, cytokines, enteroviruses, fatigue, intravenous immunoglobulin, picornaviruses, post-polio syndrome, virus persistence

part of future medicine fsg

Acute flaccid paralysis & poliomyelitis

Acute flaccid asymmetrical paralysis represents the key clinical manifestation of acute anterior poliomyelitis (AAP), an infectious encephalomyelitis caused by poliovirus (PV) types 1–3. A number of neurotropic viruses of the *Picornaviridae* family have also been implicated. Echoviruses, coxsackie A and B viruses and the new enteroviruses 70 and 71 are among the agents potentially associated with AAP [1]. In spite of the possibility that multiple pathogens cause AAP-like forms, poliomyelitis (in Greek, polios = gray + myelitis) is, by antonomasia, the acute paralytic illness associated with PV. The process is characterized by cellular inflammation and neuronal necrosis in anterior and intermediate horns of the gray matter of the spinal cord. Sporadic or wild paralytic poliomyelitis is an ancient disease, still occurring in an endemic pattern in areas where vaccination programs could not be regularly carried out [101]. Since 1894, PV epidemics became a major health concern, with hundreds of thousand dead or paralyzed victims. In 1952, the largest polio epidemic in the USA affected nearly 58,000 people [2]. Before the introduction of voluntary and statutory vaccination programs in the middle 1950s and early 1960s, over 85% of paralytic disease was caused by type-1 PV (Brunhilde), whereas two other PV (type-2 Lansing and type-3 Leon) were responsible for the remaining cases. Strikingly, in a few patients, mixed PV types have been detected. While over 90% of people exposed to PV develop unapparent infections, 4–8% show nonspecific gastrointestinal symptoms of short duration (minor illness), and 1–2% of patients develop an aseptic meningitis (major illness). In a variable number of cases, minor and major illnesses progress to paralytic disease, which is characterized by muscle pain, fasciculation, transient increase of deep reflexes and eventually asymmetrical trunk and extremities palsy (spinal form), or lower cranial nerve involvement (bulbar form). A number of dysautonomic disturbances have been reported during acute poliomyelitis. The progression of paralysis usually stops in a few days, after which there is a period of stability of variable duration followed by functional recovery of different degrees. The recovery may occur either within weeks, which suggests a revival of infected motor neurons, or within several months, as a consequence of collateral sprouting and reinnervation of muscles by unaffected and/or surviving motor neurons [3].

The introduction of vaccination caused a dramatic drop in the number of new cases and eradicated the disease in developed countries. It has also led to the appearance of a new form of paralysis associated with vaccine-derived polioviruses. This form has been found both in vaccinated subjects and in nonimmune individuals exposed to the live oral PV vaccine [4]. Poliomyelitis is still endemic in several countries, with Afghanistan, Pakistan, India and Nigeria accounting for the majority of cases (1,873 cases in 2006) [101]. Ten to 20 million individuals who survived poliomyelitis epidemics are still alive worldwide [102]. The number of polio survivors is approximately 1 million in the USA [103] and about 300,000 in Europe. Survivors of acute paralytic polio have attracted the attention of health professionals and policy-makers, since they may develop a constellation of highly stereotyped new symptoms decades after the acute illness.

The first description of this syndrome, characterized by late-onset weakness, progressive paresis and muscular atrophy, has been reported in two French patients. The disorder was later termed chronic anterior poliomyelitis by Oppenheim [5]. Over the last 20 years, there has been an increasing awareness of this neurological condition, which is now termed post-polio syndrome (PPS).

PPS: definition & diagnostic criteria

PPS is a new neurological disorder that occurs in a large proportion of polio survivors. As opposed to acute poliomyelitis, a disorder predominantly affecting male subjects, PPS may have a predilection for females [6–9]. The cardinal clinical features of PPS are new weakness, muscular fatigability, general fatigue, cramps, cold intolerance and musculoskeletal pain [6,10]. Muscular symptoms involve previously affected segments, but also regions spared by the acute illness. A number of diagnostic criteria for the clinical diagnosis of PPS have been proposed following the original ones of Mulder and coworkers in 1972 [11]. Recently, a European Federation of Neurological Societies task force has recommended the adoption of the criteria proposed by Halstead in 1985 and 1991 [6,12,13]. These criteria, mostly based on clinical studies, have been further revised by the March of Dime Birth Defects Foundation [104], and can be summarized as follows:

- Confirmed history of paralytic poliomyelitis with asymmetric flaccid paresis, evidence of motor neuron loss with residual weakness and muscle atrophy, and signs of denervation/reinnervation on electromyography;
- A period of partial to complete neurological recovery after acute paralysis, followed by functional and neurological stability of 15 years or more;
- Persistent new muscle weakness or decreased muscle endurance of gradual/sudden onset, with or without muscle atrophy, musculoskeletal pain or generalized fatigue;
- Symptoms persisting for at least 1 year;
- Exclusion of other conditions as a cause of symptoms.

The use of the above criteria has led to the recognition of PPS as a new entity and has increased the awareness that a number of distinct causes responsible for functional impairment in patients with prior poliomyelitis are potentially treatable. However, it should be noted that assessing functional stability in young patients may be difficult, until transition from puberty into adulthood is attained. In addition, in several cases the interval between acute illness and functional deterioration is shorter than 15 years. Therefore, diagnostic criteria for PPS should be revised accordingly. To date, the etiology of PPS remains elusive. Population studies have estimated the prevalence of PPS among polio survivors to be between 15 and 80% [9,14–18]. Both clinical and population studies have assessed a high incidence of new systemic, neurological and muscular complaints in individuals with previous poliomyelitis, the frequency of which shows variations probably due to a lack of homogeneity among different studies (**Table 1**) [9,16,19–27].

Risk indicators & clinical manifestations

Numerous risk factors for the development of PPS have been reported. These include older age at the onset of poliomyelitis (as a likely effect of decreased neuronal plasticity and diminished ability to recover with increasing age) [6,28], and longer times to recover from the acute illness, which represents an indicator of underlying compensatory mechanisms following acute disease [14,29,30]. Accordingly, a short time interval (usually a few weeks) suggests the functional recovery of affected neurons. By contrast, recovery within or after the first year of illness is indicative of muscle innervation by collateral sprouting or hypertrophy of muscle fibers, respectively. The severity of the residual paralysis has been considered an additional risk factor for the development of PPS. However, patients with nonparalytic disease are also at risk of developing PPS, but at a reduced frequency compared with those with paralytic illness. The ongoing chronic loss of motor neurons can only be compensated by collateral nerve sprouting and muscle hypertrophy. Therefore, new muscle weakness is clinically manifest when failure of the above compensatory mechanisms occurs. One of the most accepted pathogenetic hypotheses for new weakness postulates distal motor unit degeneration and defective neuromuscular transmission [31,32].

The clinical manifestations of PPS are classically distinguished as neurological, musculoskeletal and general [10,29,33]. Neurological manifestations include new muscle weakness and atrophy, bulbar muscle involvement, respiratory failure, sleep disturbances, cold intolerance and peripheral/central fatigue. Musculoskeletal symptoms consist of muscle and joint pain, in addition to skeletal

Table 1. Clinical manifestations in post-polio syndrome.

Study	Joint pain	Generalized fatigue	Muscle pain	Weakness in muscles		Total new	Atrophy	Cold intolerance	Dyspnea	Bulbar muscle involvement	Sleep disturbances	Impaired attention/ word finding difficult	Ref.
				Previously affected	Previously unaffected								
Ramlow J *et al.* 1992 **n** = 551	34	40	34	35	NA	NQ	11	24	NA	NA	NA	NA	[9]
Lonnberg F 1993 **n** = 3067	62	51	33	NA	54	33	NA	42	NA	NA	NA	NA	[16]
Halstead S *et al.* 1995 **n** = 132	89	71	71	NA	69	50	28	29	NA	NA	NA	NA	[19]
Agre JC *et al.* 1996 **n** = 79	83	77	86	80	53	87	39	56	39	30	NA	NA	[20]
Kidd *et al.* 1997 **n** = 239	7	37	37	NA	NA	32	NA	NA	4	NA	9	NA	[21]
Wekre LL *et al.* 1998 **n** = 1444	57	57	58	NA	85	58	NA	62	43	NA	48	39	[22]
Ivanyi B *et al.* 1999 **n** = 233	44	33	34	NA	NA	58	30	NA	18	17	NA	NA	[23]
Jubelt B, Agre JC 1999 **n** = 200	85	73	74	88	60	93	55	51	39	32	NA	NA	[24]
Rekand T *et al.* 2000 **n** = 148	52	42	56	NA	NA	67	30	NA	41	NA	14	NA	[25]

Data are expressed in %.

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				Previously affected	Previously unaffected								
Chang CW, Huang SF 2001 **n =** 31	68	31	23	NA	NA	100	NA	NA	0	NA	NA	NA	[26]
Farbu E *et al.* 2003 **n =** 85	57	34	44	NA	NA	79	80	NA	35	NA	37	NA	[27]
Fiorini M *et al.* Present study **n =** 16	76	53	29	88	53	90	40	70	0	0	29	NA	

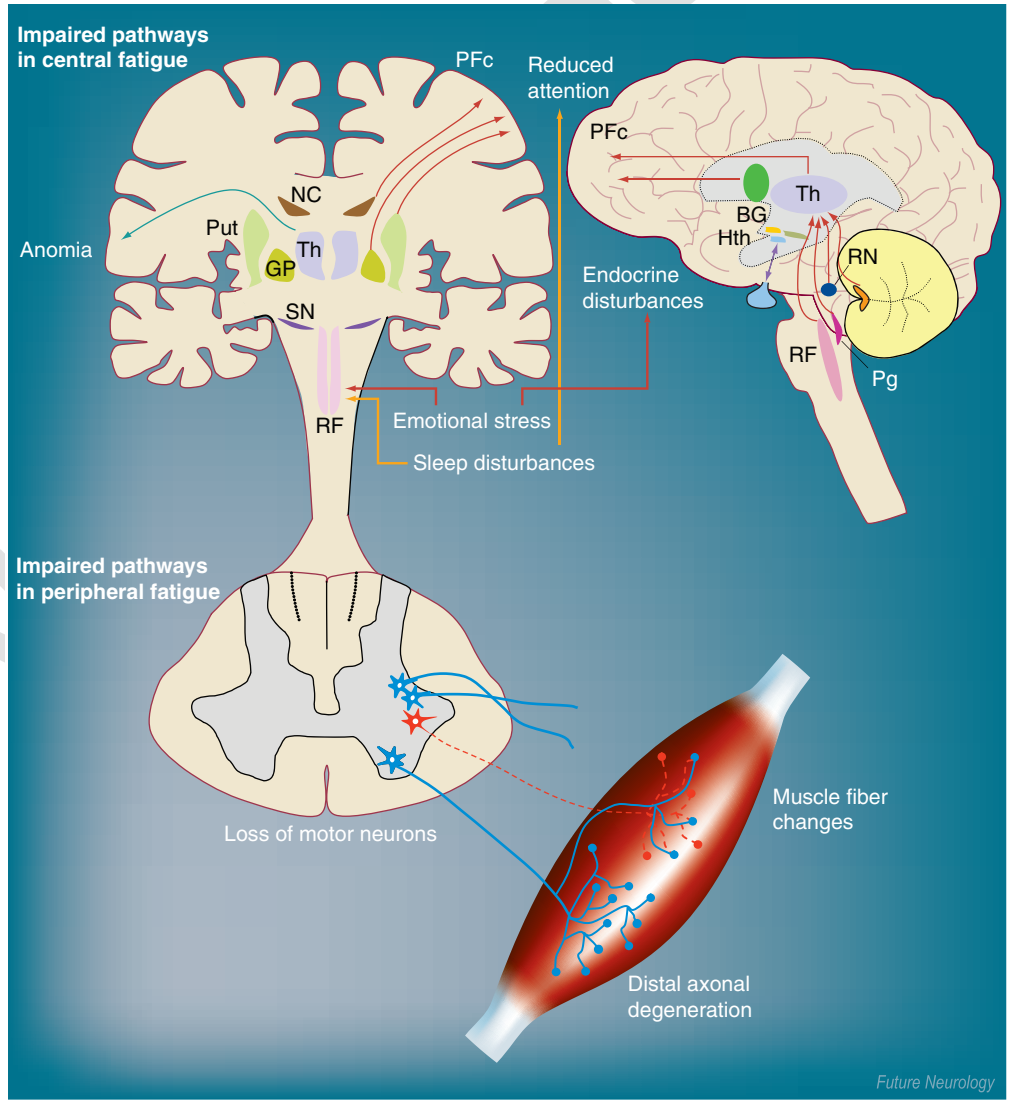
Data are expressed in %.

distortion with secondary nerve and nerve root entrapment or compression. General manifestations encompass general fatigue and cardiorespiratory deconditioning. Fatigue represents a common and highly disabling complaint in PPS patients and is often referred to as an increasing muscle weakness or loss of strength during exercise. It may have general, central or peripheral causes (**Figure 1**).

Generalized fatigue may be related to a reduction of cardiorespiratory function, as an effect of low activity level (cardiorespiratory deconditioning) and decreased aerobic power [34,35]. This symptom can improve through aerobic exercise [36] or endurance training [37].

In addition to generalized fatigue, nearly 90% of patients with either paralytic or non-paralytic polio experience difficulty in initiating or maintaining voluntary activities, a condition that has central origin and that can be accompanied by neuropsychological dysfunction [38]. Central fatigue involves an impaired recruitment of functioning motor units and a diminished fire frequency of these units [39,40]. Central fatigue is perceived as a sensation of physical exhaustion and, when severe, is associated with deficits on attention tests, impaired concentration [38], altered speed of information processing, anomia and word-finding difficulty,

Figure 1. Anatomical sites and neural pathways involved in post-polio fatigue.



BG: Basal ganglia; GP: Globus pallidus; Hth: Hypothalamus; NC: Nucleus caudatus; PFc: Prefrontal cortex; Pg: Periaqueductal gray matter; Put: Putamen; RF: Reticular formation; RN: Red nucleus; SN: Substantia nigra; Th: Thalamus.

in the absence of cognitive ability or verbal memory impairment. The exact pathogenic mechanisms responsible for central fatigue remain obscure. However, PV damage to dopaminergic pathways, the ascending reticular activating system, putamen and globus pallidus, thalamus, hypothalamus and cortical motor areas are held responsible for the development of central fatigue [41]. Generally speaking, central fatigue represents the final effect of a disturbed integration, during physical activities, between sensory and motor pathways on one hand and cognitive processing on the other [42,43]. The involvement of cortical areas and some subcortical nuclei is in keeping with the observation that PPS patients with fatigue present slow-wave abnormalities on electroencephalographic recordings. Additional factors responsible for central fatigue have been claimed to include the effect of increased production of inflammatory cytokines, possibly associated with hypofunctional hypothalamic–pituitary–adrenal axis [44] or increased intrathecal expression of cytokines. Finally, peripheral fatigue likely occurs as a result of chronic denervation with a reduced number of fibers, in addition to muscle or neuromuscular junction impairment [43], and is more readily measured as a reduction of force during maximum voluntary muscle contraction. A number of sleeping problems, including sleep apnea, nocturnal myoclonus, periodic limb movements and restless leg syndrome, have been reported in PPS patients [45]. A large percentage of these patients report cold-related attacks of burning pain, hyperesthesia and color changes in affected limbs. During the attack, patients report decreased muscle strength and impaired dexterity. This condition has been termed cold-intolerance and is thought to represent a form of complex regional pain syndrome due to dysfunction of neuronal cells of the intermediolateral column [46]. In patients with PPS, new weakness may be a transient phenomenon and manifests itself as muscle fatigability. In other cases, weakness is a permanent symptom and is usually asymmetric, involving previously affected but also unaffected muscles, either proximal or distal. Weakness may develop subacutely or in a slowly progressive manner, although a stepwise progression can be observed. In patients with bulbar poliomyelitis, PPS may present with respiratory insufficiency, dysarthria, dysphagia and dysphonia.

Electrophysiological studies

Electrodiagnostic studies provide valuable diagnostic information in patients with antecedent poliomyelitis. However, electrophysiological findings are of no help in separating patients with asymptomatic stable polio from those with PPS. Therefore, the main role of clinical neurophysiology is to provide confirmatory evidence of motor neuron loss and to rule out coexisting neuromuscular diseases. Typical findings observed on conventional electromyography (EMG) include [10,13,31]:

- Huge and polyphasic motor unit potentials (MUPs), due to compensatory reinnervation;
- Fibrillations and positive sharp waves at rest, which are generated by chronic or recent denervation;
- Reduction of the interference EMG pattern during voluntary muscle contraction due to a drop in motor unit number.

In addition, owing to the instability and remodeling of surviving motor units, following repetitive stimulation the shape of MUPs may change (jiggle) [47]. The neurophysiological study of individual motor units by single fiber EMG (SFEMG) discloses [10]:

- Increased fiber density
- Increased jitter (the time interval between the action potential generated by two muscle fibers belonging to the same motor unit) during voluntary muscle activity
- Blocking, or failure to induce an action potential in a single fiber on repeated stimulation

Taken together, jiggle, increased jitter and blocking are indicative of neuromuscular endplate instability due to impaired neuromuscular transmission in fibers undergoing continuous denervation and reinnervation processes. Additional neurophysiological methods include macro-EMG, a modified SFEMG technique that is useful in detecting and measuring the reinnervation process by collateral sprouting, and methods for estimating motor neuron number [48].

Pathological studies

Pathological examination of the spinal cord of patients with previous poliomyelitis has disclosed loss of motor neurons, neuronal atrophy, active gliosis and perivascular/parenchimal/meningeal cellular inflammation, both in patients with new weakness or in subjects with stable postpoliomyelitis deficits [49]. Inflammatory infiltrates are usually composed of T and B cells, although a

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

Disorder	Positive/negative 14-3-3 assay	Ref.
Viral meningoencephalitis	2/7	[68]
	12/24	[69]
Nonviral meningoencephalitis	3/11	[68]
	12/20	[70]
Multiple sclerosis	1/10	[68]
	0/8	[69]
	5/38	[71]
	3/37	[72]
	25/114 (ELISA)	[73]
	24/63	[74]
	14/16	[75]
Alzheimer disease	1/49	[69]
	4/20	[76]
Other dementias	0/5	[68]
	0/14	[69]
	4/31	[76]
Stroke	4/8	[69]
Paraneoplastic diseases	10/70	[77]
Guillain–Barré syndrome	0/5	[68]
	29/38	[78]
Motor neuron disease	0/7	[68]
Noninflammatory neuropathy	0/16 (ELISA)	[73]

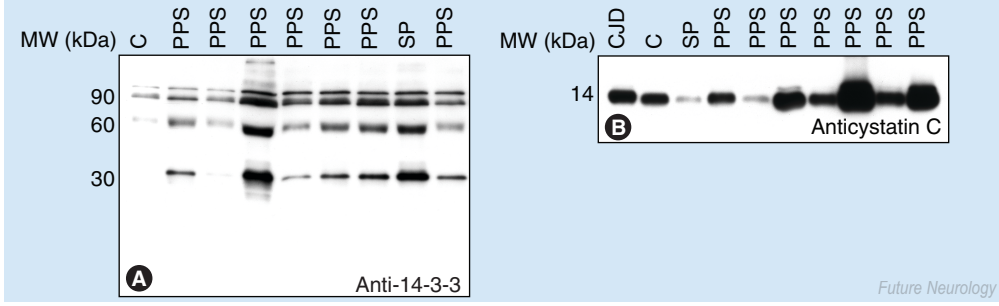
ELISA: Enzyme-linked immunosorbent assay.

single case with exclusive B-cell infiltration has been reported [50]. Notably, Fishman found no evidence of inflammation in seven spinal cords of poliomyelitis survivors [51]. In subjects with new symptoms, the pathological picture was characterized by the presence of axonal spheroids and neuronal chromatolysis, changes regarded as a sign of neuronal dysfunction following increased functional demand [49]. This could, however, not be the case, since recent experimental evidence suggests that axonal swellings occur in viral and autoimmune disorders of the CNS following cytotoxic T-lymphocyte attack [52]. Therefore, pathogenic mechanisms leading to spheroid formation in PPS could primarily involve virus-induced and/or immune-mediated mechanisms. In parallel with findings obtained in spinal cords, the study of muscle biopsies from patients with postpoliomyelitis muscular atrophy has disclosed patterns characterized by signs of recent and old denervation, with variable degrees of reinnervation in recently weakened muscles. The same findings were present both in originally involved and in spared muscles. Perivascular and interstitial $CD4^+$ and $CD8^+$ T-cell infiltration was detected in approximately 40% of the cases. Conversely, only moderate degrees of reinnervation, without denervation and mononuclear cell infiltration, was observed in stable post-polio patients [53].

Laboratory studies

To date, the diagnosis of PPS relies predominantly on clinical criteria. Blood tests are essentially normal, with the exception of increased levels of creatine kinase that is observed in a minority of cases [54,55]. Several studies have suggested that the host immune response may be critical in PPS pathogenesis. However, studies initiated to assess the role of antibody response to PV (either circulating or cerebrospinal fluid

Figure 2.



(A) Detection of 14-3-3 protein in 25 µl of cerebrospinal fluid in patients with PPS, SP and in a control subject after immunoblot with antipan 14-3-3 polyclonal antibody at a 1:500 dilution. **(B)** Detection of cystatin C in 2.5 µl of cerebrospinal fluid of patients with PPS and SP as compared with control and CJD subjects. Blot exposed to an anticystatin C polyclonal antibody at a 1:1000 dilution, followed by an enhanced chemiluminescent system.
C: Control subject; CJD: Creutzfeldt–Jakob disease; PPS: Post-polio syndrome; SP: Stable polio.

[CSF] antibody), have provided conflicting results. In addition, studies purporting an altered phenotypic expression of circulating T cells and the detection of antiganglioside and antineurofilament IgM antibodies remain to be confirmed [56,57]. By contrast, clear evidence of increased CSF levels of the proinflammatory cytokine IL-2 and its receptors has been provided [58]. These studies point to chronic T-cell activation. In addition, independent studies have demonstrated an augmented systemic and intrathecal expression of TNF-α, IFN-γ, IL-4 and -10 mRNA transcripts [59]. Recent studies have shown a selective increase of TNF-α in the CSF of PPS patients [60]. It was, however, not clarified whether a connection between PV infection and immune deregulation existed. Among the mechanisms considered for PV-induced immunopathological changes, the hypothesis that persistent viral infection plays a major role has been considered since the early description of PPS cases. Accordingly, experimental and clinical evidence of persistent nonlytic mutants of PV in neuronal cell lines and CSF from PPS patients has been obtained [61–64], although some authors have reported negative results [65]. These findings, if confirmed in a large number of cases, could provide a rationale for the use of antienteroviral drugs. Autoimmune mechanisms have also been considered. These include bystander activation of pre-primed autoreactive T cells by antigen-presenting cells and, less likely, molecular mimicry-mediated injury.

Searching for markers of PPS

While little doubt exists that immune deregulation plays a role in PPS, it is still unknown whether dysimmune mechanisms leading to increased cytokine expression reflect a chronic process or a recent-onset process. In previous studies that documented an increased cytokine mRNA expression and increased TNF-α levels [59,60], it was not evaluated whether the observed upregulation could also be detected in patients with stable polio. The investigated population, in fact, included only PPS patients. As a part of a large study still in progress, we recently tried to address this issue by investigating 19 consecutive patients (three with stable polio and 16 with PPS). Three protein markers were dosed in CSF samples: 14-3-3, cystatin C and tau.

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

Patient No.	Diagnosis	Age (years)	CSF protein level (mg/dl)	Oligoclonal Bands	Tau (pg/ml)	1D PAGE 14-3-3	2D PAGE high molecular weight 14-3-3	Cystatin C*
1	Post-polio	52	0.24	nd	374	±	+	0.16
2	Post-polio	73	0.85	nd	115	±	+	0.98
3	Post-polio	50	0.41	nd	<60	±	+	0.22
4	Post-polio	58	0.87	nd	199	+	+	4.66
5	Post-polio	81	0.66	nd	210	+	+	nd
6	Post-polio	57	0.25	nd	<60	±	+	nd
7	Post-polio	52	0.35	nd	198	±	+	1.37
8	Post-polio	66	0.37	+	174	-	+	0.91
9	Post-polio	65	0.37	nd	167	±	+	nd
10	Post polio	51	0.37	nd	195	±	+	nd
11	Post-polio	51	0.24	nd	198	-	+	nd
12	Post-polio	73	0.25	nd	160	±	+	0.32
13	Polio	75	0.15	nd	401	±	+	0.56
14	Post-polio	60	0.21	nd	63	±	+	0.36
15	Polio	54	0.20	+	<60	+	+	0.19
16	Post-polio	54	0.27	nd	86	nd	+	1.99
17	Post-polio	52	0.24	nd	331	nd	+	7.5
18	Post-polio	62	0.22	nd	345	nd	+	11.77
19	Polio	62	0.30	nd	390	+	+	0.15

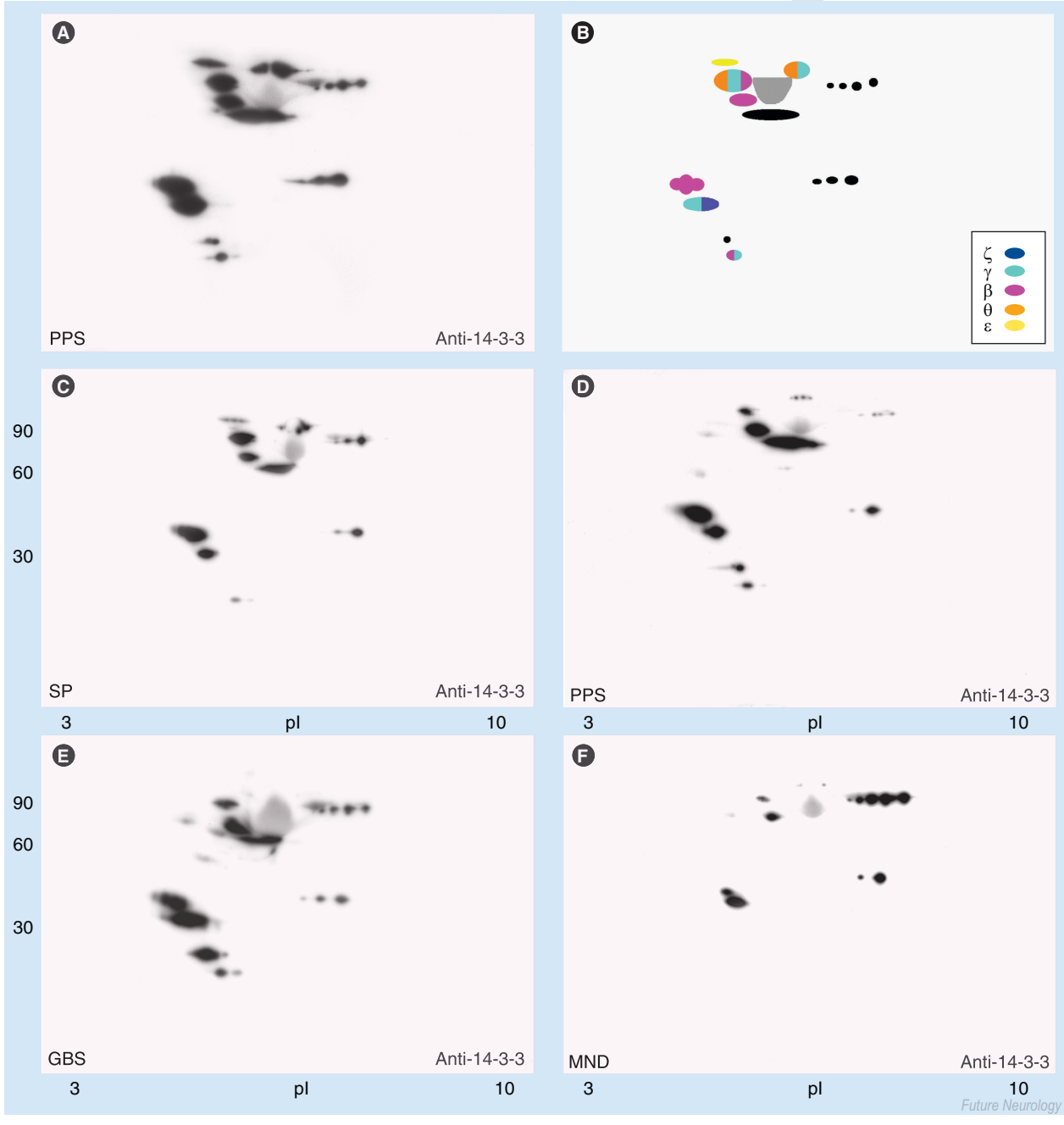
**Band optic density compared with the mean of controls in arbitrary units.*

CSF: Cerebrospinal fluid; nd: Not determined; PAGE: Polyacrylamide gel electrophoresis .

The 14-3-3 proteins are a family of low molecular weight proteins encompassing seven isoforms (β, γ, ε, η, ζ, σ and θ) that are particularly abundant in the nervous system [66] and are involved in cell locomotion, cellular signaling and inflammation. Different lines of evidence suggest that 14-3-3 proteins also have anti-inflammatory functions that may counteract the biological action of metalloproteinases, chemokines and proinflammatory cytokines [67].

The 14-3-3 proteins have been investigated in CSF samples of patients with different neurological disorders (**Table 2**), with widely different results and possible interpretations [68–78]. While long considered a marker of axonal damage, more recent data indicate that 14-3-3 proteins are markers of inflammatory CNS disorders [75,78]. The data in **Table 3** and **Figure 2** show that using the conventional 14-3-3 assay, moderate to strong positivity was detected in three patients with

Figure 3.



stable polio and in nine patients with PPS. Five PPS patients were 14-3-3-negative. However, when immunoblot was performed after two-dimensional (2D)-polyacrylamide gel electrophoresis (a method significantly increasing the sensitivity of 14-3-3 detection) all patients were strongly 14-3-3-positive. As shown in **Figure 3**, a quite complex pattern of isoforms was observed. Two series of spots at approximately 30 and 33 kDa, with pIs in the pH range 4.5–5.5, followed by a series of spots at 60 and 90 kDa distributed over a wider pI interval. Conversely, control samples showed no detectable spots of 14-3-3. The present results show that increased levels of 14-3-3 are found in both stable polio and PPS patients. The pattern reported here is similar to that seen in patients with multiple sclerosis and inflammatory polyradiculoneuropathy, but differs from that observed in neurodegenerative disorders such as Creutzfeldt–Jakob disease and amyotrophic lateral sclerosis [75,79]. Based on the peculiar isoform pattern encountered in stable polio and PPS patients, it seems likely that 14-3-3 protein in the CSF derives from astrocytes and microglia/mononuclear cells.

These preliminary findings suggest that ongoing CNS inflammation does occur in patients with antecedent polio, regardless of the clinical expression of PPS. The observed normal levels of the tau protein in both groups suggest that the

Executive summary

Acute flaccid paralysis

- The three poliovirus serotypes of the *Enterovirus* genus and other neurotropic viruses of the *Picornaviridae* family are the cause of infectious paralytic encephalomyelitis.
- A new form of paralytic illness has been reported in vaccinated and nonimmune individuals exposed to the live oral poliovirus vaccine.

Post-polio syndrome

- Post-polio syndrome (PPS) is a new neurological disorder occurring in polio survivors at least 15 years after recovery from acute paralysis.
- Diagnosis of PPS is based on clinical criteria.

Clinical manifestations of PPS

- PPS causes neurological, musculoskeletal and general symptoms. Fatigue, muscle weakness, cold intolerance, joint and muscle pain are the main disabling complaints.
- Increased frequency of sleep disturbances, including sleep apnea, nocturnal myoclonus, periodic limb movement disorder and restless leg syndrome, have been reported in patients with PPS.

Electrophysiological findings in PPS

- Electrophysiological studies are of no help in separating patients with PPS from those with stable polio.
- Neurophysiological studies provide evidence of motor neuron loss and to rule out coexisting neuromuscular disorders.

Pathological & laboratory findings in PPS

- Active cellular inflammation has been documented in spinal cords of subjects with antecedent poliomyelitis, either with stable polio or with PPS.
- Patients with PPS have increased intrathecal levels of the cytokine IL-2 and its receptor, in addition to augmented systemic and cerebrospinal fluid expression of other proinflammatory cytokines.
- Independent laboratories have detected poliovirus genome fragments in the cerebrospinal fluid of a large number of post-polio patients.

Cerebrospinal fluid markers in PPS & subjects with stable polio

- Increased levels of 14-3-3 protein are observed in the cerebrospinal fluid of both stable polio and PPS patients.
- Proteomic and isoform patterns of 14-3-3 protein are highly suggestive of ongoing inflammatory changes either in PPS or in stable polio individuals.
- Cerebrospinal fluid levels of the microtubule-associated tau protein are within the normal range. On the contrary, cystatin C expression is either decreased or increased.

Future diagnostic & therapeutic perspective

- Intravenous immunoglobulin is partially effective in increasing muscle strength and in improving the quality of life in PPS patients.
- Findings on viral persistence encourage the design of treatments aimed at the administration of antiviral drugs.
- Proteomic investigations appear to be very promising tools for the identification of reliable cerebrospinal fluid markers and for the development of rational therapies.

inflammatory process is not accompanied by rapid neuronal/axonal destruction. Finally, the wide variation observed for cystatin C levels in CSF samples encourages us to pursue additional analyses of this marker in a larger group of patients. While the downregulation of cystatin C observed in five cases, is in keeping with similar observations in inflammatory CNS disorders, the marked upregulation observed in three PPS patients remains to be explained.

Taken together, the present results suggest that the use of the above CSF markers may be of value for therapeutic decisions regarding post-polio patients, regardless of clinical PPS expression.

Future perspective

To date, a number of pharmacological treatments have been proposed for PPS. Some have been evaluated with variable results [80–85]. More recently, a randomized, controlled trial has showed increased muscle strength and improved quality of life (paralleled by decreased expression of cytokines in the CSF) in PPS patients treated with IVIg [86].

In addition to the evidence of increased cytokine expression, the detection of PV genomes in the CSF of subjects with antecedent polio [61–64] further encourages investigations of antiviral drugs possibly associated with immune-modulating agents [64].

While the pathogenetic mechanisms triggering the clinical manifestation of PPS remain elusive, our preliminary data suggest that inflammatory changes may also be operative in the CNS of patients with stable polio. Therefore, longitudinal studies of inflammatory markers, cytokine expression and viral markers in the CSF of large numbers of patients should provide information on the preclinical or subclinical neurological involvement in patients with antecedent polio. These investigations may lead to the development of rational therapies for PPS patients.

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