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ORIGINAL ARTICLE

Post-polio syndrome is not a dysimmune condition

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ABSTRACT

BACKGROUND: Poliomyelitis is a global disabling disease affecting 12-20 million of people. Post poliomyelitis syndrome (PPS) may affect up to 80% of polio survivors: increased muscle weakness, pain, fatigue, functional decline. It relies on aging of an impaired neuro-muscular system with ongoing denervation processes. A late involvement of humoral or cellular pro-inflammatory phenomena is also suspected.
AIM: To assess the dysimmune hypothesis of PPS by comparing lymphocyte subpopulations and humoral immune factors between PPS patients and controls.
DESIGN: Cross-sectional study.
SETTING: Montpellier University Hospital.
POPULATION: Forty-seven PPS and 27 healthy controls.
METHODS: PPS patients and controls were compared on their lymphocyte subpopulations and humoral immune factors (IL-1β, IL-6, IL-8, IL-17, IL-21, IL-22, IL-23, IFN-γ, TNF-α, GM-CSF, RANTES, MCP1, MIP-3a, IL-10, TGF-β, IL4, IL13). Patients were further compared according to their dominant clinical symptoms. Sample size guaranteed a power >90% for all comparisons.
RESULTS: PPS patients and controls were comparable in gender, age and corpulence. Most patients had lower limb motor sequelae (N.=45, 95.7%), a minority had upper limb motor impairment (N.=16, 34.0%). Forty-five were able to walk (94%), 35/45 with technical aids. The median of the two-minute walking test was 110 meters (interquartile range 55; 132). Eighteen (38%) required help in their daily life. Their quality of life was low (SF36). All described an increased muscular weakness, 40 (85%) a general fatigue, and 39 (83%) muscular or joint pain. Blood count, serum electrolytes, T and B lymphocyte subpopulations and cytokines were comparable between patients and controls, except for creatine phospho kinase that was significantly higher in PPS patients. None of these variables differed between the 20/47 patients whose late main symptoms were pain or fatigue, and other patients.
CONCLUSIONS: Our results suggest that PPS is not a dysimmune disease.
CLINICAL REHABILITATION IMPACT: Our results do not sustain immunotherapy for PPS. Our work suggest that PPS may be mostly linked to physiological age-related phenomena in a disabled neuromuscular condition. Thus, our results emphasize the role of prevention and elimination of aggravating factors to avoid late functional worsening, and the importance of rehabilitation programs that should be adapted to patients' specific conditions.

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KEY WORDS: Postpoliomyelitis syndrome; Physiopathology; Immunity; Lymphocytes; Cytokines; Muscle weakness.

Poliomyelitis is a global disabling disease affecting 12-20 million of people.[1, 2] Currently, thanks to the preventive vaccination campaigns, the Eastern Mediterranean region (Afghanistan and Pakistan) remains the main part of the world that is not free of wild poliovirus.[3]

At the chronic phase, a recent epidemiological review suggests an average worldwide prevalence of 295/100,000, that may be over-estimated.[4] Although the prevalence of poliomyelitis sequelae is decreasing in Europe and in the USA, it remains very high in developing countries[5] which constitutes a global concern for the next decades. Indeed, among polio survivors, post poliomyelitis syndrome (PPS) resulting in functional decline may affect up to 80% of them.[6] PPS diagnosis relies on Halstead criteria.[7] The main symptom is the gradual appearance of muscles weakness or fatigability after a period of stable neuromuscular function in patients with prior paralytic poliomyelitis. Patients can also experience various symptoms affecting different motor or non-motor functions, especially pain or fatigue. PPS is a clinical diagnosis, requiring excluding any medical or orthopedic conditions as causes of symptoms. The severity and the time course evolution of the symptoms may vary among patients.[8] These impairments can lead to severe decrease in functioning with important consequences on quality of life.

The prevalence of PPS may increase in the world in the next few decades, rendering its treatment very important, especially in emerging countries were poliomyelitis has been lately eradicated. Symptomatic and rehabilitative treatments are efficient but could be improved by specific treatments targeting the pathological mechanisms underlying PPS.

PPS pathophysiological explanations are still unclear and several hypotheses have been formulated.[5] First, PPS results from the aging of an impaired neuro-muscular system with ongoing denervation/reinnervation processes and stress-induced degeneration of surviving neurons. In this case, PPS is considered as a consequence of a gradual motor unit failure due to multiple factors like physiological aging, metabolic exhaustion, and overuse.[6] This motor unit failure is superimposed with age-related sarcopenia and changes in contractile properties of muscular fibers contributing to muscular fatigue and myalgia. Another hypothesis that could explain part of the symptoms of PPS relies on the persistence or reactivation of the polio virus in the central nervous system[9-12] leading to a late increase in humoral and/or cellular pro-inflammatory phenomena.[13, 14] This dysimmune hypothesis is sustained by some studies showing an abnormal increased level of pro-inflammatory cytokines and molecules both in blood[15-17] and cerebral spinal fluid,[18] and inflammatory changes in central nervous system and muscles biopsies.[19, 20] It is currently admitted that the increase in pro-inflammatory cytokines may contribute to damage neurons through the release of oxidative agents and glutamate.[17] In that context, intravenous immunoglobulins have been tested to improve patients with PPS,[21] with inconclusive results. This hypothesis of an immune-mediated disease could also open up key therapeutic perspectives based on drugs affecting the immune-response such as monoclonal antibodies. This hypothesis remains highly controversial to date.[22]

Therefore, this study aimed at comparing lymphocyte sub-populations and humoral immunity between PPS patients and controls, expecting to provide evidence of the dysimmune hypothesis of PPS. Based on previous studies suggesting a link between clinical presentation of patients and level of pro-inflammatory cytokines in the blood,[17] we also studied subpopulations of PPS patients to compare the same variables according to the dominant symptoms (pain and/or fatigue *versus* other symptoms).

Materials and methods

Study design

This monocentric prospective study was carried out in Montpellier university hospital, France, from December 2017 to March 2020. We included adult patients with PPS and healthy controls. Recruitment of controls was stratified by gender and age to match the gender and age distribution of patients with PPS. The study protocol was approved by the Comité de Protection des Personnes Nord-Ouest III (chairperson: Mme Charlotte Gourio) on 13/05/2017, before the experiment was started (protocol number: 2017-13). It was registered on ClinicalTrials.gov (NCT03396783). The study has been conducted in accordance with the declaration of Helsinki, and all participants signed a written informed consent form.

Participants

Eligible patients were those above 18 years with a diagnosis of PPS made by a Physical and Rehabilitation Medicine (PRM) physician, according to Halstead *et al*. criteria: 1) prior infection with poliovirus with initial motor impairment confirmed by medical history, residual motor deficit and muscle atrophy on clinical examination, and possibly signs of denervation on electromyography; 2) a full or partial recovery period after the initial acute phase, with neu-

rological and functional stability for at least 15 years; 3) a subsequent gradual or rapid loss of muscle strength and/or endurance with or without new recent muscle atrophy, generalized fatigue, muscle or joint pain; other rarer symptoms may also be noted (sleep disorders, breathing difficulties, dysphagia, dysarthria, etc.); 4) these symptoms are unusual and long-lasting, evolving over more than one year; 5) alternative medical causes that may be responsible for the various symptoms have been ruled out.

Control subjects were eligible if they were above 18 years and had no history of acute poliomyelitis. They were recruited among family members of other inpatients from the PRM department.

Non-inclusion criteria for both patients and controls were all pathologies or treatments that could distort the clinical and immunological profile: intercurrent neurological pathology; uncontrolled cardiovascular risk factors (unbalanced diabetes with HbA_{1c} >7%, obesity with Body Mass Index >35 kg/m^2, hypertriglyceridemia or hypercholesterolemia, heart failure); pulmonary comorbidity (Chronic obstructive pulmonary disease or asthma requiring disease-modifying treatment); previous endocrine disorders such as thyroid damage; anemia; systemic inflammatory pathology, autoimmune disease or sicca syndrome; renal failure (creatinine clearance < 60ml/min); anti-inflammatory treatment in progress or in the previous month, immunoregulatory treatment whatever its nature; patients with PPS who received polyvalent IV immunoglobulins in the previous 3 years; vaccination in the previous month.

Clinical assessment

Clinical assessment was made in the group of patients with PPS by the PRM physician. Main symptoms (muscular weakness, general fatigue or muscular/joint pain), ability to walk and autonomy for daily activities were assessed through clinical examination and patient interview. The patients also answered self-questionnaires about pain, fatigue and quality of life.

Further clinical assessment was carried out by a physiotherapist. It included a 2-minute walking test[23] to measure the distance covered in 2 minutes at a comfortable speed. Muscle strength was assessed using the Manual Muscle Testing described by Mendell *et al.*,[24] scoring each muscle from 0 (no contraction) to 5 (normal force against strong resistance applied by the evaluator) for six lower limb muscles (gluteus maximus, hip flexors, quadriceps, tibialis anterior, hamstrings, triceps surae) and four upper limb muscles (shoulder abductors, elbow flexors, elbow extensor, wrist extensors) on both sides. We calculated a score summing the results of the 12 lower limb muscles (therefore ranging from 0 to 60) and a score summing the eight upper limb muscles (ranging from 0 to 40). A higher score indicated stronger muscles. In addition, grip strength was assessed on both sides with a Jamar Test.[25]

Biological dosages

In both groups, the immunological profile was assessed by peripheral blood sampling. An EDTA tube (3 mL) was used for lymphocyte phenotyping in order to quantify the T lymphocyte subpopulations (Th1, Th2, Th17, regulatory T cells), as well as B and NK lymphocytes. Phenotyping was performed by flow cytometry (Navios-Beckman Coulter cytometer). The results were expressed in percent of total lymphocytes and in absolute values. In addition, a dry tube (5 mL) was first centrifuged and the sera obtained were stored at -80°C for further analysis. Measurement of the serum concentration of an extended profile of blood cytokines and chemokines including proinflammatory cytokines (IL-1β, IL-6, IL-8, IL-17, IL-21, IL-22, IL-23, IFN-γ, TNF-α, GM-CSF, RANTES, MCP1, MIP-3a), anti-inflammatory cytokines (IL-10, TGF-β), and others (IL-4, IL-13), was carried out remotely with assay by Luminex® technique (Fidis™-Theradiag). Lastly, a peripheral blood sample (7 mL in total) on EDTA tube and heparinized tube was performed for complete blood count (hematology laboratory), CRP and CPK measurement (biochemistry laboratory).

The primary endpoint was defined as the immunological profile of participants, consisting of the blood concentrations of the cytokines studied, as well as the rate and absolute number of the different peripheral blood lymphocyte populations (T-lymphocyte subpopulations, B and NK lymphocytes).

Self-questionnaires

Patients filled in the following self-questionnaires.

Self-Reported Impairments in Persons with Late Effects of Polio (SIPP)[26]

Patients rated the impact of thirteen PPS-related symptoms (muscle fatigue, muscle weakness, pain, etc.) over the past two weeks on a scale ranging from 1 (not at all) to 4 (extremely): maximum score 52.

Visual Analogue Scale (VAS) for pain

Patients assessed their general level of pain during the last week on a scale ranging from 0 (no pain) to 100 (maximal pain).

Fatigue Severity Scale (FSS)[27]

Patients rated nine items ranging from 1 (minimum) to 7 (maximum) to assess their level of fatigue. The total score ranged from 9 to 63.

Fatigue Impact Scale (FIS)

This self-questionnaire assesses the effect of fatigue on activities of daily living over the last month. Patients rated 40 items from 0 to 4 corresponding to three subscales: physical, cognitive and social. A high score corresponds to greater fatigue, with a maximum possible score of 160. This scale is validated in French in multiple sclerosis.[28, 29]

Short-Form 36 (SF-36)

This 36-item generic scale measures health-related quality of life in eight dimensions, each ranging from 0 to 100. Two composite scores can be calculated: a physical component summary (mean 50 in the general population) and a mental component summary score (mean 50 in the general population). A higher score indicates a higher quality of life. It has been validated in various diseases.[30]

Statistical analysis

In previous studies comparing PPS patients and healthy controls, the smallest significant difference was the TNF-α concentration: 18.2 *vs.* 12.2 pg/mL, with a common standard deviation of 3.3 pg/mL.[15, 31] We applied the Bonferroni correction to test 24 biological values, and calculated that we needed 14 patients per group to have a 90% power to show a significant difference (with a corrected alpha risk of 0.002) in any of these biological values. We decided *a priori* to increase this number to 50 PPS patients and 40 controls, to obtain more reliable descriptive data.

We described patients with PPS and controls using mean and standard deviation or median and interquartile range (IQR) for quantitative variables, and number and percentages for qualitative variables. Comparisons of quantitative variables between patients and controls were based on Student's *t*-tests or Mann-Whitney Tests, and comparisons of qualitative variables were based on chi square tests or Fisher's Exact Test. The same methods were used to compare patients according to their dominant clinical symptoms (pain or fatigue *versus* other symptoms). Missing data were not replaced. Statistical analyses were performed using SAS Enterprise Guide, version 4.3 (SAS Institute, Cary, NC, USA) and Stata, SE 15.0 (StataCorp LCC, College Station, TX, USA).

Data availability

Individual participant data that underlie the results reported in this article can be made available upon reasonable request to the corresponding author.

Results

Patients and clinical description

We recruited 74 participants, including 47 patients and 27 controls. Patients and controls were comparable in gender (64% female *vs.* 56% respectively, P=0.48), age (mean±SD: 61±9 *vs.* 60±10, P=0.64) and corpulence (Body Mass Index 25.3±4.3 kg/m^2 *vs.* 25.9±5.0, P=0.72). Clinical characteristics and questionnaires' results of the 47 patients with PPS are described in Table I. Most patients had lower limbs motor sequels (45, 95.7%), a minority upper limb motor impairment (16, 34.0%). Forty-five were able to walk (94%), of which 35/45 with technical aids. The median of the two-minutes walking test was 110 meters (IQR 55; 132). Eighteen (38%) required help

TABLE I.—*Characteristics of the patients with post-poliomyelitis syndrome (PPS).*

Variable	N.	PPS patients (N.=47)
Symptoms		
Muscular weakness	47	47 (100%)
General fatigue	47	40 (85%)
Muscular/joint pain	47	39 (83%)
Time since new symptoms onset (years)	46	9.5 (3; 15)
Able to walk	47	44 (94%)
2-min walking test, distance (meters)	43	110 (55; 132)
Grip strength, right hand (Jamar)	46	22 (18; 32)
Grip strength, left hand (Jamar)	46	24 (17; 29)
Motor testing, upper limbs (max 40)	45	38 (31; 39)
Motor testing, lower limbs (max 60)	46	23 (17; 31)
SIPP (max 52)	38	34 (30; 42)
VAS for pain (max 100)	46	43 (20; 70)
Fatigue Impact Scale (FIS)		
Cognitive dimension	43	23 (16; 30)
Physical dimension	42	41 (37; 44)
Social dimension	41	33 (23; 38)
Psychological dimension	42	11 (8; 12)
Total score (Max 160)	39	108 (86; 124)
Fatigue Severity Scale (FSS)		
Total score (min 9, max 63)	39	47 (37; 55)
Quality of life (SF-36)		
Physical Component Summary (mean 50 in the general population)	38	31.1 (27.7; 36.7)
Mental Component Summary (mean 50 in the general population)	38	40.1 (33.6; 50.1)

Values are median (interquartile range) unless otherwise stated.
SIPP: Self-Reported Impairments in Persons with Late Effects of Polio; VAS: Visual Analogue Scale.

TABLE II.—*Blood count and serum electrolytes in patients with post-poliomyelitis syndrome (PPS) and controls.*

Variable	PPS patients (N.=46)	Controls (N.=27)	P value
Hemoglobin (g/dL)	14.5 (13.6; 15.1)	14.8 (14.0; 15.5)	0.42
MCV (fl)	92 (89; 95)	94 (91; 97)	0.25
Platelet count (10^9/L)	252 (215; 298)	238 (206; 278)	0.60
Leucocytes (10^9/L)	6.43 (5.48; 6.96)	6.68 (5.78; 8.15)	0.19
Neutrophils (%)	58.5 (51.0; 63.0)	57.0 (51.0; 62.0)	0.87
Eosinophils (%)	3.5 (2.0; 5.0)	3.0 (2.0; 4.0)	0.39
Basophils (%)	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	0.67
Lymphocytes (%)	28.5 (25.0; 37.0)	31.0 (26.0; 38.0)	0.79
Monocytes (%)	8.0 (6.0; 9.0)	7.0 (6.0; 9.0)	0.77
CRP (mg/L)	2.0 (0.9; 3.2)	1.4 (0.8; 2.3)	0.37
CPK (UI/L)	139 (79; 196)	93 (61; 140)	0.01

MCV: mean corpuscular volume; CRP: C-reactive protein; CPK: creatine phospho kinase. Values are median (interquartile range). Blood sample analysis was missing for one PPS patient.

in their daily life. Their quality of life assessed with the SF-36 questionnaire was low. All described an increase in muscular weakness, 40 (85%) a general fatigue, and 39 (83%) muscular or joint pain.

Biology

Blood counts and serum electrolytes were comparable between patients and controls, except for creatine phospho kinase that was higher in PPS patients (Table II). Lymphocyte counts, comprising a fine analysis of the subpopulations of T lymphocytes (Figure 1) (Supplementary Digital Material 1: Supplementary Table I), and cytokine and peptides dosages (Figure 2) (Supplementary Digital Material 2: Supplementary Table II) were comparable between the two groups.

Blood counts, T lymphocytes and cytokine or peptide levels were also compared between patients whose late main symptoms were pain or fatigue (N.=20) and other PPS patients (N.=27). None of the variables differed clinically between the two groups (Supplementary Digital Material 3: Supplementary Table III and IV).

Discussion

Summary of the results

Our study aimed to explore the dysimmune hypothesis of PPS in the scope of developing specific treatments in the context of an epidemiological global emergency. Our results did not show any difference in cellular nor humoral immunity between 47 PPS patients and 27 age-matched controls, based on blood analysis of lymphocyte counts

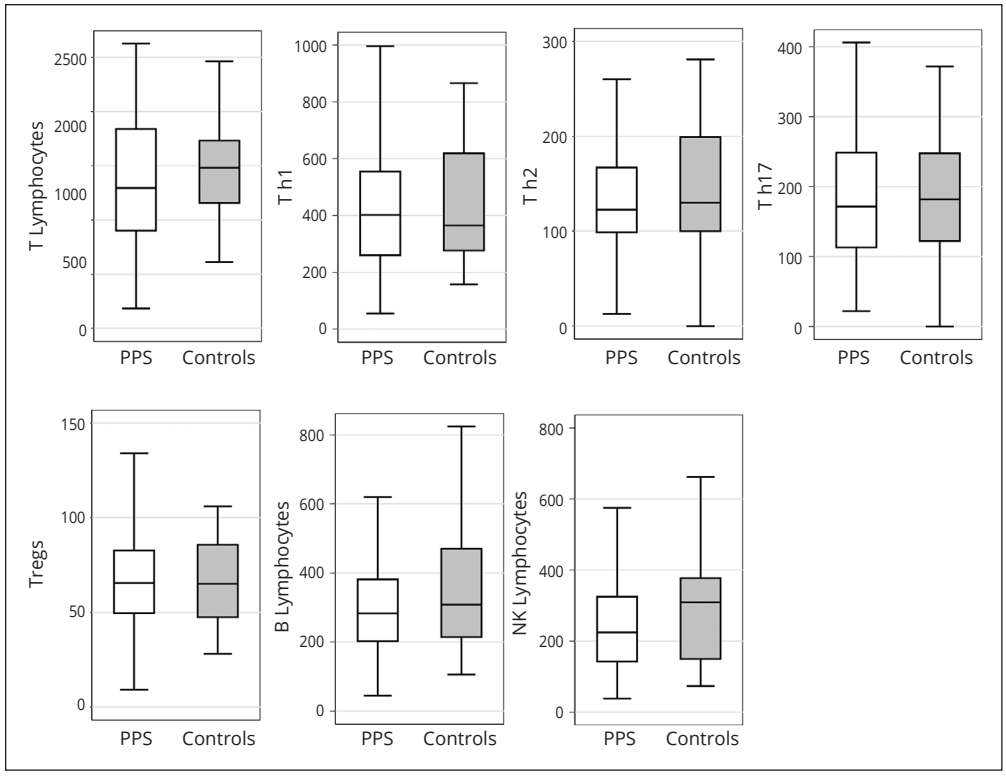

Figure 1.—Box plots representing lymphocyte levels in patients with PPS (N.=47) and controls (N.=25).
Tregs: Regulatory T lymphocytes. Lymphocytes counts are expressed in N/mm³. Data were missing for 2 out of 27 subjects in the control group. Box plot interpretation: the medium line represents the median value, the box represents the first and third quartiles, and whiskers represent minimum and maximum adjacent values. Outliers are not plotted. Exact values are given in Supplementary Digital Material 1.

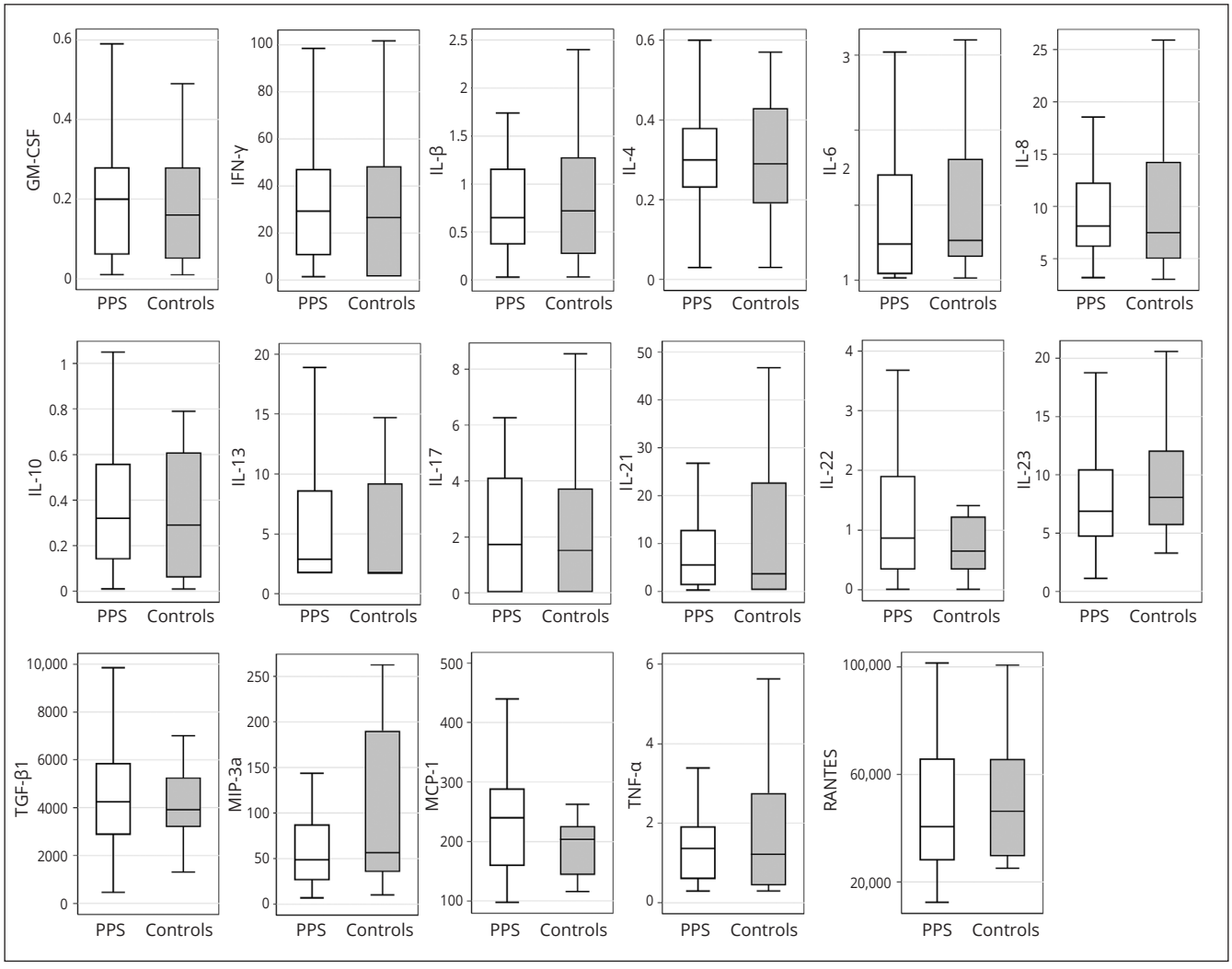

Figure 2.— Box plots representing cytokine levels in patients with PPS (N.=47) and controls (N.=25). Cytokine levels are expressed in pg/mL. Data were missing for two out of 27 subjects in the control group. Box plot interpretation: the medium line represents the median value, the box represents the first and third quartiles, and whiskers represent minimum and maximum adjacent values. Outliers are not plotted. Exact values are given in Supplementary Digital Material 2.

and on dosage of pro- and anti-inflammatory cytokines and peptides. Subgroup analysis failed to demonstrate different immunological profiles of patients depending on their clinical presentation.

These results are conflicting with the results from Fordyce[17] who conducted the main similar study in 2008 on 56 PPS patients and 26 controls. They concluded that TNFα levels, as well as IL-6 and leptin were significantly increased in patients compared to controls. They also demonstrated that the elevated TNFα levels in PPS were associated with increased muscle pain. Since their method was very similar to ours, such differences could be linked to other bias – inclusion of patients with confusing other diseases leading to the increase of immunological markers, differences in dosage kits and reliability of their results – or to chance.

Medical literature sustaining the dysimmune origin of the PPS is questionable

Over the past 30 years, some studies have shown an abnormally high level of pro-inflammatory cytokines or peptides in the blood or in the cerebrospinal fluid (CSF) of PPS patients (Table III).[13, 15-18, 31-35] These results are con-

TABLE III.—*Studies on blood and CSF dosages of pro-inflammatory and anti-inflammatory cytokines and peptides in PPS patients*[13, 15-18, 31-35] *and on muscle histological or biological changes in PPS.*[19, 20, 32, 36]

Reference	Method	Patients	Controls	Results	Conclusion
Blood and CSF dosages of cytokines and peptides in PPS patients					
Dalakas 1986[32]	CSF immunologic dosages	27 PPS		Oligoclonal bands (IgG) were found in the cerebrospinal fluid of 7 of 13 patients studied.	Controversial
Sharief 1991[18]	CSF	36 PPS	13 stable poliomyelitic patients + 18 ALS + 36 other neuromuscular disease	Oligoclonal IgM were found in 58% of PPS and none of controls, and were poliovirus-specific. CSF levels of IL-2 and soluble IL-2 receptors were higher in PPS patients than in controls. Results support intrathecal immune response to poliovirus, suggesting new or persistent poliovirus infection in the CNS of PPS.	In favor
Roivainen 1994[35]	CSF	21 PPS		No poliovirus-specific IgM Antibodies in the CSF of PPS patients	Negative
Gonzalez 2002[16]	CSF and blood	13 PPS	8 non-inflammatory controls + 7 multiple sclerosis	Increased expression of inflammatory cytokines (TNF-α, IFN-γ, IL-4, IL-10) in CSF (but not in peripheral blood) of PPS compared to non-inflammatory controls. The increase was comparable to that of multiple sclerosis, a well-known neuroinflammatory disease.	In favor
Gonzalez 2004[33]	CSF and Blood	16 PPS before and after IVIG treatment	26 patients with non-inflammatory other neurological diseases	TNF-alpha, IFN-gamma and IL-10 CSF mRNA levels were elevated in untreated persons with PPS compared to other neurological diseases. Upon IVIG treatment, IFN-gamma and TNF-alpha mRNA levels were reduced, while IL-10 remained unchanged.	In favor
Fiorini 2007[13]	CSF	16 PPS	3 stable poliomyelitic patients	Inflammatory changes occur in both stable polio and PPS: *14-3-3* increased in both groups; *Tau* was within normal range; *Cystatin C* was non interpretable.	Controversial
Fordyce 2008[17]	Blood	51 PPS patients	26 healthy controls	TNFα levels, as well as IL-6 and leptin were significantly increased compared to controls. The elevated TNFα levels in PPS were associated with increased muscle pain.	In favor
Gonzales 2012[31]	Blood + CSF	20 with IVIG	30 with other neurological diseases	At baseline (before IVIG), TNF and IFN-γ in CSF and peripheral blood were higher in PPS patients than in controls. One year after IVIG, PPS patients had beneficial changes in cytokine profiles with decreased IFN-γ and IL23 + increased anti-inflammatory IL-13 in CSF	In favor
Melin 2014[34]	Blood	20 PPS	95 healthy controls	No increase in circulating immune complex or in TNF-inducing effects of circulating immune complex	Negative
Bickerstaffe 2015[15]	Blood	45 PPS	18 healthy controls	IL-6, IL-8, TNF-α and leptin increased in PPS patients compared to controls but no evidence for an association between inflammation and clinical deterioration was found. Other inflammatory mediators (IL-10, IL-18 and IL-13) did not differ.	Controversial
Inflammatory infiltrates in muscles of PPS patients					
Dalakas 1986[32]	Muscle biopsies	27 PPS		The newly affected muscles evaluated longitudinally showed chronic and new denervation.	Negative
Dalakas 1988[20]	Muscle	27 PPS	5 stable poliomyelitic patients	Perivascular or interstitial inflammatory cells (predominantly lymphocytes unrelated to phagocytosis) were noted in 40% of all PPS patients. The newly weakened muscles show signs of recent denervation.	Controversial
Borg 1988[36]	Muscle	19 PPS	4 patients with radicular lesions	Non-specific changes in fiber type composition with transition of type 2 to type 1 muscle fibers with marked hypertrophy.	Negative
Melin 2014[19]	Muscle	8 PPS	6 healthy controls	Higher expression of enzymes of the prostaglandin E2 synthetic pathway, in muscle from PPS patients, compared with controls. Evidence for an inflammatory process of the muscle, which could be secondary to systemic inflammation.	Controversial

ALS: amyothrophic lateral sclerosis; CNS: central nervous system; CSF: cerebrospinal fluid; IVIG: intravenous immunoglobulin.

troversial, mostly because of the small sample size of the populations studied, and because some of them reported conflicting negative results.

Other studies reported the existence of inflammatory infiltrates in the skeletal muscles of PPS patients, none of them being able to conclude if the results were due to a general inflammatory process or to muscles overuse (Table III).[19, 20, 32, 36]

Medical literature sustaining the persistence or reactivation of the poliovirus in the CNS is controversial

Initially, these dysimmune hypotheses were based on previous works suggesting persistence or reactivation of polio virus (PV) in the CNS of patients with PPS (Table IV).[10-12, 18, 32, 37-39] Starting with an old experimental animal study showing that poliovirus may cause persistent infec-

TABLE IV.—*Studies searching for the persistence or reactivation of the poliovirus in the CNS.*[10-12, 18, 32, 37-39]

Reference	Patients	Controls	Method	Results	Conclusion
Dalakas 1986[32]	27 PPS		CSF virologic dosages	No elevation of antibodies to poliovirus was observed in the CSF	Negative
Sharief 1991[18]	36 PPS	13 stable poliomyelitic patients + 18 ALS + 36 other neuromuscular diseases	CSF dosages	Oligoclonal IgM were found in 58% of PPS and 0 of controls, and were poliovirus-specific. CSF levels of IL-2 and soluble IL-2 receptors were higher in PPS patients than in controls. Results support intrathecal immune response to poliovirus, suggesting new or persistent poliovirus infection in the CNS of PPS	In favor
Melchers 1992[39]	16 PPS	25 other neurological diseases	PCR and IgM antibody-capture enzyme-linked immunosorbent assay. Blood, CSF and muscles biopsies.	Poliovirus RNA or a poliovirus type-specific IgM response was detected in none of the specimens.	Negative
Dalakas 1995[37]	Un-known		Histopathology, histochemistry, Immunocytochemistry, PCR, lymphocytes counts, virological searches.	Presence of poliovirus in the spinal fluid of 4/40 PPS patients, in the peripheral blood lymphocytes of 7/37 PPS patients, and not in muscle. Their role in the pathogenesis of PPS is unknown	Controversial
Muir 1995[12]	24 PPS	36 stable poliomyelitic patients + 36 other neurologic conditions	PCR in CSF (Viral RNA)	3/24 ongoing PPS patients and 0 control patient had positive PCR	Negative
Jubelt 1995[38]	146 PPS patients from 7 studies		Review of previous poliovirus antibody studies in PPS	1 positive study (21/36 patients) and 6 negative studies	Negative
Leparc 1996[11]	10 PPS	10 ALS + 10 other neurological disease + 3 stable poliomyelitic patients	Genomic sequences CSF / reverse transcription PCR	Poliovirus-specific genomic sequences in the 5* untranslated region and in the capsid region (VP1) were detected in 5/10 PPS patients but in 0/23 control patient.	Controversial
Julien 1999[10]	20 PPS	20 unrelated neurological diseases + 7 stable poliomyelitic patients	RT-PCR	Poliovirus genomic sequences were detected in the CSF of 11/20 PPS patients and in none of the control group	Controversial

ALS: amyothrophic lateral sclerosis; CSF: cerebrospinal fluid.

TABLE V.—*Review of studies exploring CNS morphological or biological changes in PPS patients.*[13, 41-43]

Reference	Patients	Controls	Method	Results
Pezeshkpour 1988[43]	3 PPS patients	10 ALS + 5 spino-cerebellar degeneration patients + 5 stable polio	Sections of spinal cord histology	Atrophy of motor neurons, severe reactive gliosis, and mild to moderate perivascular and interparenchymal inflammation. No difference between PPS patients and stable ones.
Fiorini 2007[13]	16 PPS patients	3 stable polio	CSF proteins: 14-3-3, cystatin C, and tau	Inflammatory changes occur in both stable polio and PPS: 14-3-3 increased in both groups; Tau was within normal range; Cystatin C was non interpretable.
Gonzales 2009[41]	15 PPS patients	9 healthy + 34 other non-inflammatory diseases + 17 secondary progressive multiple sclerosis	CSF protein biomarker	Differential expression of gelsolin, hemopexin, and kallikrein 6 in PPS patients compared to controls.
Li Hi Shing 2021[42]	36 polio survivors	88 ALS + 117 healthy		Cortical and white matter reorganisation in poliomyelitis survivors which may be interpreted as compensatory, change in response to severe lower motor neuron injury in infancy.

ALS: amyothrophic lateral sclerosis; CSF: cerebrospinal fluid.

tion and paralysis upon immunosuppression in mice,[40] the possible pathogenic role of a persistent PV infection and its related chronic inflammation due to the upregulation of pro-inflammatory cytokines and chemokines has been suggested. Currently, studies in this field are sparse and weak.[9]

Arguments sustaining CNS morphological or biological changes in PPS patients suggesting an evolutive process

Some authors conducted biochemical, histological or anatomical studies in PPS patients that could indirectly sustain the hypothesis of a potentially age-related, neurodegenerative, or dysimmune evolving pathology of the CNS (Table V).[13, 41-43] These studies are scarce and non convincing.

Strengths and limitations of the study

Our study recruited one of the largest samples described in this research field. We carefully selected patients with confirmed PPS, and without alternative inflammatory disease. Controls were healthy subjects, frequency matched on age and sex. A large subset of humoral and cellular inflam-

matory markers was analyzed. However, our study may present limitations. This was a monocentric study – but we are a regional reference center. We recruited prevalent cases – but as this syndrome does not spontaneously heals, nor leads to death, we do not feel that this would select a particular subgroup of patients; and as the PPS tends to worsen over years, it would be surprising that an initial inflammatory syndrom had disappeared, which explains our negative results. Lastly, we did not reach the intended sample size because of recruitment difficulties. However, the statistical power was guaranteed because we included 47 and 27 patients, and both groups were comparable in age and sex.

Conclusions

Our study does not confirm the dysimmune hypothesis of the post-poliomyelitis syndrome. It reinforces the idea that these clinical manifestations may be linked to neurological aging phenomena that could be explored by the dosages in blood or CSF of specific biomarkers or abnormal proteins known to be involved in different pathways associated with tissue damage and apoptosis.[41] If confirmed, they would open the door for biological or drug neuroprotective treatments. These results also reinforce the importance of PRM care and cure with preventive and curative strategies, whose effectiveness has been widely documented in the literature:[8] prevention of secondary complications, rehabilitation, adjustments to living conditions.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
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