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Elevated plasma inflammatory mediators in post-polio syndrome: No association with long-term functional decline

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ABSTRACT

A key feature of post-polio syndrome (PPS) is progressive loss of muscle strength. In other chronic diseases systemic inflammation has been linked to muscle wasting. In this study plasma TNF-α, IL-6, IL-8, and leptin levels were significantly increased in PPS-patients compared to healthy controls. There was however no association between these raised systemic levels of inflammatory mediators and long-term decline in quadriceps strength or other clinical parameters. In conclusion, there is evidence for systemic inflammation in PPS, yet the relationship with clinical deterioration remains tenuous.

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1. Introduction

Post-polio syndrome (PPS) is a neuromuscular disease characterised by slow progressive loss of muscle strength and increased muscle fatigability reflecting ongoing motor unit loss and degeneration (March of Dimes, 2000, Bickerstaffe et al., 2014, Mccomas et al., 1997, Koopman et al., 2015). Furthermore, PPS-patients frequently suffer from complaints such as fatigue and generalised pain (Nollet et al., 1999, Halstead and Rossi, 1985). The cause of these motor unit changes and associated morbidities years after the acute infection is not well understood. It has been proposed that both chronic systemic and localised inflammatory processes are involved (Dalakas, 2002).

Studies to date have found evidence of local inflammation and immunological responses in the central nervous system (Miller, 1995, Pezeshkpour and Dalakas, 1988, Dalakas et al., 1986, Sharief et al., 1991, Farbu et al., 2007, Gonzalez et al., 2004, 2002, muscle (Dalakas, 1988, Melin et al., 2014) and vascular system (Dalakas, 1987, Ginsberg et al., 1989) of PPS-patients. Also, the presence of inflammatory markers and mediators in peripheral blood of PPS-patients indicates systemic immunological activation (Farbu et al., 2007, Fordyce et al., 2008, Gonzalez et al., 2004, 2002, 2012). The reasons for this immune activation and the connection between local or systemic inflammation and clinical manifestations of the disease however remain unresolved. There is some evidence for a possible relationship of inflammatory mediator levels with pain and with self-reported physical functioning, but none with muscle strength, fatigue or walking capacity (Dalakas, 2002, Farbu et al., 2007, Fordyce et al., 2008, Gonzalez et al., 2012, Werhagen and Borg, 2011). In studies examining mRNA expression of major pro-inflammatory mediators in central nervous system, TNF-α and IFN-γ expression declines after intravenous immunoglobulin treatment (Gonzalez et al., 2004). However, the reported effects of this immunoglobulin treatment on symptoms vary, with a meta-analysis revealing inconsistent effects on muscle strength and no effect on pain or activity limitations (Koopman et al., 2015). Lack of correlations and inconsistent results in these studies might be explained by the great variation in mediators and substrates studied, clinical tests used and control groups included in each study (Dalakas, 2002, Farbu et al., 2007, Fordyce et al., 2008, Gonzalez et al., 2004, 2012, Werhagen and Borg, 2011, Koopman et al., 2015). No study so far has evaluated a large selection of inflammatory mediators, the relationship between inflammatory mediator levels and motor unit changes, or the relationship between inflammatory mediator levels and the rate of clinical decline.

In this study we aimed to verify evidence for systemic inflammation in PPS-patients using a panel consisting of 3 different groups of mediators: (i) pro-inflammatory, (ii) anti-inflammatory, and (iii) immune-modulatory. This broad panel included key mediators representative of specific inflammatory pathways allowing analysis of the pathways potentially involved in the immune response in PPS. Furthermore, we aimed to determine whether patients with evidence of inflammation were also those with the highest rate of clinical deterioration, i.e. a faster rate of decline in quadriceps strength, motor unit size, or physical mobility over the previous 10 years.

Abbreviations: PPS, post-polio syndrome; MU-size, motor unit size; MUAPs, single motor unit action potentials; mRNA, messenger RNA; CNS, central nervous system.

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2. Methods

2.1. Subjects

The PPS-cohort has been described in detail elsewhere (Bickerstaffe et al., 2014, Bickerstaffe et al., 2015). Sixty-six adults with PPS that had completed baseline measurements in a randomised controlled trial of pyridostygmine between 1999 and 2001, were invited to participate in the present study, 10 years later (Horemans et al., 2003). At baseline, all individuals had PPS, with symptoms of post-poliomyelitis muscle dysfunction in either or both quadriceps muscles (March of Dimes, 2000). They also showed evidence of neuromuscular transmission defects on single-fibre EMG, indicative of ongoing denervation and reinnervation, and had no important comorbidities. Detailed in- and exclusion criteria are described elsewhere (Horemans et al., 2003). New exclusion criteria were the presence of any newly developed disease that affected voluntary control of the muscles, immunological diseases and the use of immune-regulatory medication. Eighteen healthy controls, gender-matched and in the same age range as the PPS-patients, were selected from a larger pool of healthy volunteers who donated blood to the hospital laboratory in 2010 for reference value determination. The healthy controls were not subjected to any other clinical tests.

All participants provided written informed consent, and the institutions' Medical Ethics Committee approved the study.

2.2. Study design and measurements

In this cohort study, all PPS participants underwent a standardised assessment of functioning on two separate days, in most cases within two weeks and never more than 3 months apart. This assessment was performed in the same way at baseline and follow-up. Day 1 encompassed an intake and physical examination, completion of questionnaires and a walking capacity test. On day 2, isometric strength measurements and high-density surface EMG measurements were performed on the strongest symptomatic quadriceps muscle as measured at baseline. Longitudinal changes in strength and motor unit size (MU-size) have been reported elsewhere (Bickerstaffe et al., 2014, 2015). Peripheral blood samples for haematological and inflammatory mediator analysis were taken on day 1 — before any activity measurements — at follow-up only. Healthy controls underwent venepuncture only.

2.2.1. Analyses of inflammatory mediators

Peripheral blood was collected from PPS participants and healthy controls in EDTA to prevent clotting. First, 200 μl of each blood sample was removed for haematological analysis of leukocyte counts and differentiation. Then, the remainder of the sample was centrifuged for 10 min at 1700 $\times g$ and plasma was aliquoted and stored at −80 °C until analysis. This procedure was completed within 1 h 30 min after venepuncture to limit bias by prolonged incubation with blood cells. A panel of twelve mediators were determined using luminex (Bioplex, BioRad, Veenendaal, The Netherlands) according to the manufacturer's instructions. This panel was chosen to distinguish mediators active in different immune pathways. The panel consisted of the following: (i) pro-inflammatory mediators: interferon-γ (IFN-γ), IL-1α, IL-1β, IL-6, IL-8, leptin and tumour necrosis factor-α (TNF-α); (ii) anti-inflammatory mediators: IL-1RA and IL-10; and (iii) immune-modulatory mediators: IL-13, IL-17A and IL-18. The stored plasma samples from PPS-patients and healthy controls were analysed in parallel.

2.2.2. Clinical measures

2.2.2.1. MU-size. High-density surface EMG was used to estimate MU-size. The measurement and analysis protocol has been described extensively previously (Bickerstaffe et al., 2014, Drost et al., 2004). Briefly, a rectangular electrode grid composed of 130 gold-coated electrodes (electrode diameter: 1.5 mm; interelectrode distance: 5 mm), was placed over the vastus lateralis muscle, such that 10 columns with 13 electrodes each were positioned parallel to the muscle fibres. A reference electrode was placed on the patella. Monopolar signals were stored for offline analysis after the required amplification and filtering procedures (Bickerstaffe et al., 2014). Single motor unit action potentials (MUAPs) were extracted from bipolar EMG recordings of five, 30-s contractions between 5% and 20% of peak knee extension strength using a semi-automated software programme (Gligorijevic et al., 2013). MUAP-size of each unique MUAP was then calculated from the area under the curve of 50 ms of the monopolar signal from the electrode nearest to the endplate zone. The mean MUAP-size was then calculated for each patient at baseline and follow-up.

2.2.2.2. Quadriceps strength. Peak knee extension strength (Nm) was defined as the strongest of three isometric maximal voluntary contractions performed on a hard surfaced fixed chair dynamometer with knee and hip flexed at 90°.

2.2.2.3. Walking capacity. The distance walked (m) in 2 min at a comfortable pace on a standardised 50 m oval circuit was recorded (Stolwijk-Swuste et al., 2008). Participants used the same assistive walking devices they used in daily life.

2.3. Statistics/data analysis

The main outcome measures were circulating levels of the 12 measured mediators (i.e. IFN-γ, IL-1α, IL-1β, IL-1RA, IL-6, IL-8, IL-10, IL-13, IL-17A, IL-18, TNF-α and leptin) (pg/ml), mean MUAP size (mV∗ms), knee extension strength (Nm) and walking capacity (m). Means with standard deviations (SD), medians with interquartile range [IQR], and percentages were used to describe the population. For levels of inflammatory mediators that were below the detection level, we used half the value of the lower limit of detection in the statistical analyses. Differences between levels of inflammatory mediators of patients and controls were tested non-parametrically using Mann–Whitney U test because of unequal variances between the groups. Interrelations between levels of different mediators, included to investigate which pathways might be active in PPS, were tested using Pearson correlations. Interrelations between levels of mediators and leukocyte cell counts and of mediators and BMI were also tested using Pearson correlations. These assessments were included to check if increased numbers of white blood cells and/or fat cells could underlie abnormal levels of inflammatory mediators in this group. Associations between mediator levels and clinical parameters were analysed by comparing the rate of change in clinical parameters of those with mediator levels above and below the p75 control value for that mediator (Mann–Whitney U). Only those mediators that were significantly increased in PPS-patients were analysed in this way. Statistical analysis was performed with the SPSS statistical software package (version 20.0.0.1). Significance was set at $p = 0.05$.

3. Results

3.1. Subjects

Forty-six patients with PPS agreed to participate with the inflammatory mediator measurements. Non-participants were untraceable ($n = 6$), deceased ($n = 2$), unwilling/unable ($n = 6$), or excluded for (i) co-morbidities that may have affected the quadriceps under investigation ($n = 4$), (ii) immunological disease (i.e. chronic lymphocytic leukaemia) ($n = 1$), and (iii) use of anti-inflammatory drug prednisone ($n = 1$). Analyses of plasma samples were completed for all 18 healthy controls and 45 PPS-patients. Due to clotting of the blood sample, inflammatory mediator analysis was not reliable for the remaining PPS-participant. Incomplete data on clinical

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