Progressive post infectious neurological syndromes with a poor outcome: long term follow-up and neurofilament light chain quantification

Pietro Businaro MD[1,2], Riccardo Currò MD[1], Elisa Vegezzi MD[1,2], Luca Diamanti PhD[2], Paola Bini MD[2], Giuseppe Cosentino PhD[1,3], Enrico Alfonsi MD[3], Lisa Maria Farina MD[4], Elena Colombo MD[5], Eleonora Tavazzi MD[5], Andrea Cortese PhD[1,6], Silvia Scaranzin[7], Matteo Gastaldi PhD[2,7], Enrico Marchioni MD[2*]

1. Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

2. Neuroncology Unit, IRCCS Mondino Foundation, Pavia, Italy.

3. Clinical Neurophysiology Unit, IRCCS Mondino Foundation, Pavia, Italy.

4. Advanced Imaging and Radiomics Center, Neuroradiology Department, IRCCS Mondino Foundation, Pavia, Italy

5. Multiple Sclerosis Center, IRCCS Mondino Foundation, Pavia, Italy.

6. Department of Neuromuscular Diseases, University College London, London, United Kingdom

7. Neuroimmunology Research Unit, IRCCS Mondino Foundation, Pavia, Italy

Corresponding author:

Enrico Marchioni MD IRCCS Mondino Foundation, via Mondino 2, I-27100

Pavia, Italy; e-mail, enrico.marchioni@mondino.it;

tel:+390382380365; fax:+390382380286

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Highlights

- Progressive-PINS are atypical demyelinating disorders with a poor-outcome
- Bulbar district is frequently affected in progressive-PINS
- Disability accumulation in progressive-PINS isn't justified by active inflammation
- Progressive-PINS are unresponsive to immunosuppressive treatments
- High levels of NfL in progressive-PINS show chronic neuronal damage

Summary

Postinfectious neurological syndromes (PINS), among which acute disseminated encephalomyelitis (ADEM), are inflammatory and mostly monophasic disorders. We previously reported that PINS patients can show relapses, or even disease progression. Here we describe a cohort of patients with progressive-PINS and >5 years of follow-up, that developed a progressive worsening without radiological/cerebrospinal fluid analysis evidence of inflammation. At onset 5 patients fulfilled diagnostic criteria for ADEM and none for MS. Progression occurred after a median of 22 months from onset (in 4/7 after 1/more relapses), manifesting as ascending tetraparesis with bulbar functions involvement in 5/7. Five/7 patients received high dose steroids and/or IvIG and 6/7 Rituximab(n=4) and/or cyclophosphamide(n=2), with no impact on disease progression in 6/7. NfL levels were higher in patients with progressive-PINS compared to monophasic-ADEM (p=0.023) and healthy controls (p=0.004). Progression is rare, but possible, in PINS. Immunotherapy seems to be ineffective in these patients, and elevated serum NfL in serum suggest persistent axonal damage.

Introduction

Post infectious/vaccination neurological syndromes (PINS) are rare and heterogeneous inflammatory conditions of the central nervous system, that include acute disseminated encephalomyelitis (ADEM). The differential diagnosis between PINS and Multiple Sclerosis (MS) is based on several clinical, laboratory and MRI features, as well as on the typical disease course, which is frequently monophasic in the former, and relapsing-remitting in the latter[1]. However, 5-30% of PINS patients can present with relapses, and rarely show a progressive course, with no evidence of laboratory/radiological inflammation (progressive-PINS) [1–3]. This entity, often associated with PNS involvement, has not been classified as a distinct pathological entity yet. In this study, we aimed to describe the long-term clinical course, outcome, and laboratory correlates of adult patients with progressive-PINS and provide biological evidence of persistent axonal damage[4].

Methods

We retrospectively screened our internal database for patients presented to our center with PINS between 2001 and 2021 (n=90). Seventy-six were excluded due to a monophasic or relapsing course. We identified 14 progressive PINS patients, 7 were excluded due to insufficient clinical information (n=4) or a follow-up < 5 years (n=3). 7 Progressive-PINS patients were included according to: a) disability increase over at least 6 months not explained by new lesions at brain and/or spinal cord MRI or inflammatory signs at CSF analysis; b) > 5 years of follow-up.

All patients were studied during the acute phase with brain and spinal cord MRI and, if PNS involvement was suspected, with electromyography/electroneurography (EMG/ENG). In addition, all patients performed a lumbar puncture at onset, at relapse (if present) and during the progressive phase. Laboratory assessment on serum and CSF included isoelectric focusing and autoantibody screening (neuronal cell-surface, anti-AQP4, anti-MOG and anti-GQ1b). Disability was assessed by means of modified rankin scale (mRS), Expanded Disability Status Scale (EDSS) and overall neuropathy limitation scale upper limbs (ONLSUL). Neurofilament light chain (NfL) levels in progressive-PINS patients and controls were measured using ELLA[5]. Statistical analysis was performed using PRISM 9 (La Jolla, CA, USA), data were compared with Mann-Whitney U test and Pearson's correlation coefficient as appropriate.

The study was conducted according to the Helsinki Declaration and approved by the Ethics Committee of the IRCCS Policlinico San Matteo (Pavia, Italy). Anonymized data of this study are available on reasonable request.

Results

Median age at presentation in progressive-PINS patients was 51 years (range 36-68) and median follow-up 98 months (range 74-233) (Table 1). Patients presented with encephalomyeloradiculitis (4), myeloradiculitis (1) and encephalomyelitis (2). None had unique-to-CSF oligoclonal bands (OCB) at onset or anti-AQP4/MOG antibodies. Six patients fulfilled the criteria for probable encephalitis[6], 5 for ADEM[7] and none those for MS. All patients received first line immunotherapy (7/7 intravenous steroids, 2/7 intravenous immunoglobulin and/or plasma exchange) at onset and showed a median improvement of 1 point in mRS scale (range 0-2) and of 2 points in EDSS scale (range 0,5-3).

The progressive course started after a median time from onset of 22 months (range 9-111), with no interposed relapses in 3/7 or after a relapsing course invariably involving the spinal cord in 4/7 patients. Disease progression was characterized by an ascending tetraparesis in all patients. Brainstem functions were affected in 5/7 patients with dysphagia, dyspnoea or both. One patient required percutaneous gastrostomy, and 2 patients needed a tracheostomy with ventilatory support (Figure 1, eFigure 1). Repeated brain and spinal cord MRI and CSF analysis did not reveal any signs of active inflammation (Figure 1, panel A,B), except for the presence of an isoelectric focusing mixed pattern in one patient. All patients presented PNS involvement, but alterations of nerve conduction parameters did not justify alone the clinical progression. No relevant comorbidities or substance abuse were reported, no precipitating factors as new infections were identified.

All patients received immunotherapy during the progressive phase. Five/7 received intravenous steroids, intravenous immunoglobulins and/or plasma exchange. Four/7 received rituximab and 2 cyclophosphamide. Overall, 6 patients presented a progressive disability accrual, one patient showed an initial improvement after starting cyclophosphamide followed by a sudden worsening (eFigure 1, panel D). Three patients died, and 4 were bedridden at the end of follow-up. Only one patient stabilized after rituximab (eFigure 1, panel A).

NfL were measured on six serum samples from progressive-PINS patients collected at a median time of 83 months (range 26-160) after disease onset and 32 months (range 4-84) after progression started. Median age at sample collection was 66 years (range 52-74). NfL levels (Figure 1, panel D) were higher in patients with progressive-PINS compared to age-matched monophasic ADEM patients (n=9; p=0.023) and healthy subjects (n=10; p=0.004). No significantly differences were detected comparing progressive-PINS with SP-MS (n=9). We found a positive (r=0.67), but not significantly, correlation between the severity of disability and Nfl values in progressive-PINS patients (eFigure 2, panel A,B).

Discussion

We describe here a subgroup of patients affected by progressive PINS with PNS involvement and more than 5 years of follow-up. A persistent axonal damage was supported by elevation of serum NfL, that was remarkable especially in 2 patients. However, this preliminary finding should be interpreted cautiously due to the low number of samples tested and to the lack of longitudinal samples.

This syndrome is characterized by a dramatic evolution, unresponsive to immune treatments, but it has not been adequately classified as a distinct condition yet among the inflammatory diseases. Although it is difficult to identify an etiological hypothesis for the small case series here presented, these patients were characterized by a clear common background, clinical picture, biological findings and poor outcome. The profile of serum NfL, the absence of OCB, MRI features and the simultaneous PNS involvement, add new clues that help identifying this syndrome as a specific pathological entity different from the classic ADEM and progressive MS.

In conclusion, progression is rare, but possible in PINS and ADEM. Aggressive immunosuppression does not seem to be helpful in these patients. Larger group of patients are needed for an exhaustive knowledge of this dramatic, often life-threatening disease.

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Figure 1. MRI at presentation (A1-4), at progression (B1-4) and clinical course of progressive-PINS patient 7 (C). Neurofilament light chain quantification in progressive PINS patients and controls (D).

(A1-2) Brain axial FLAIR images show right and left insular and bilateral pontine small hyperintensities. A3) Brain sagittal FLAIR image shows faint hyperintense signal alteration in the anterior portion of the pontobulbar passage. A4) Cervical medulla STIR-weighted image shows hyperintensity of the lateral medulla extending from C5 to C7. (B1-4) show stability of all the lesions. (C) X-axis shows the time-points in months starting from symptom onset. Green dotted bar on x-axis refer to the progressive phase. (D) Red dotted line shows lower limit of Nfl quantification. P-values were derived from Mann-Whitney test. Horizontal lines within boxes represent the median value.

ADEM: acute disseminated encephalomyelitis; EDSS: expanded disability status scale; HC: healthy control; IV6-MP: intravenous 6 metilprednisolone; mRS: modified rankin scale; ONLSUL: overall neuropathy limitation scale upper limbs; OP: oral prednisolone; RTX: rituximab; SP-MS: secondary progressive multiple sclerosis; P-PINS: progressive PINS.

eFigure 1. Individual characteristics of treatment responses and disability accumulation of progressive PINS patients 1-6 (A-F).

(A-F) X-axis shows the time-points in months starting from symptom onset. Red dotted bar on x-axis refer to the relapse. Green dotted bar on x-axis refer to the progressive phase. Black dotted vertical and horizontal lines refer to the drug treatments.

ADEM: acute disseminated encephalomyelitis; ALS: amyotrophic lateral sclerosis; AZA: azathioprine; CP: cyclophosphamide; EDSS: expanded disability status scale; HC: healthy control; IVIg: intravenous immunoglobulin; IV6-MP: intravenous 6 metilprednisolone; mRS: modified rankin scale; ONLSUL: overall neuropathy limitation scale upper limbs; OP: oral prednisolone; PLEX: plasma exchange; PT: pulsed therapy; RTX: rituximab; SP-MS: secondary progressive multiple sclerosis; P-PINS: progressive PINS.

eFigure 2. Serum NFL correlation with age, disability scale and progression time.