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RESEARCH REPORT

# Nodal–paranodal antibodies in HIV-immune mediated radiculo-neuropathies: Clinical phenotypes and relevance

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## Abstract

**Background:** The frequency of nodal–paranodal antibodies in HIV-infected patients with chronic immune-mediated radiculo-neuropathies (IMRN) has not been previously described.

**Methods:** HIV-infected patients who met the inclusion criteria for chronic IMRN were screened for immunoglobulin G (IgG) antibodies directed against nodal (neurofascin (NF)186) and paranodal (NF155, contactin-1 (CNTN1) and contactin-associated protein(Caspr1)) cell adhesion molecules, using a live, cell-based assay.

To explore potential pathogenicity, binding of human IgG to myelinated co-cultures was assessed by incubation with patients' sera positive for nodal or paranodal antibodies. Normal human serum was added as a source of complement to assess for complement activation as a mechanism for myelin injury.

**Results:** Twenty-four HIV-infected patients with IMRN were included in the study, 15 with chronic inflammatory demyelinating polyneuropathy (CIDP), 4 with ventral root radiculopathies (VRR), and 5 with dorsal root ganglionopathies (DRG). Five patients with CIDP had combined central and peripheral demyelination (CCPD). Three patients (12.7%) tested positive for neurofascin IgG1 antibodies in the following categories: 1 patient with VRR was NF186 positive, and 2 patients were NF155 positive with DRG and mixed sensory-motor demyelinating neuropathy with optic neuritis, respectively.

**Conclusion:** The frequency of nodal–paranodal antibodies is similar among IMRN regardless of HIV status. Interpretation of the results in the context of HIV is challenging as there is uncertainty regarding pathogenicity of the antibodies, especially at low titres. Larger prospective immune studies are required to delineate pathogenicity in the context of HIV, and to establish a panel of antibodies to predict for a particular clinical phenotype.

KEYWORDS
AIDP, CIDP, dorsal root ganglionopathy, HIV, immune mediated peripheral neuropathy, neuroimmunology, nodal–paranodal disease, nodopathy

## 1 | INTRODUCTION

Antibodies against neurofascin (NF), contactin-1 (CNTN1) or Caspr1, were first described in patients with the clinical diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).[1,2] However, their presence now indicates a pathologically distinct disorder, termed an autoimmune nodopathy. This emerging entity is no longer classified as CIDP as histology and response to therapy differs. Nodopathies have been described in the Western and Asian literature in <10% of HIV-uninfected cases initially diagnosed as CIDP.[3,4] Very little is known about the presence or relevance of nodal–paranodal antibodies in immune-mediated radiculoneuropathies in patients who are African in origin and are HIV infected.

The commonest chronic HIV-infected immune-mediated radiculoneuropathies (HIMRN) in our unit include CIDP, dorsal root ganglionopathy (DRG), and ventral root radiculopathy (VRR). A previous study describing CIDP and VRR, in HIV-infected patients, found that the above cohorts are highly corticosteroid (CST) responsive with shorter duration of disease, when compared with HIV-uninfected counterparts.[5,6] Some patients with autoimmune nodopathies are also steroid responsive.[3,4] NF186 and gliomedin antibodies have been described in pure motor neuropathies and NF155 in sensory ataxic neuropathies, although these serological–clinical associations are not absolute.[7] Querol et al.[1] reported patients diagnosed as CIDP with mild to moderate immunoglobulin G (IgG) reactivity against DRG and motor neurons, respectively with no identifiable antigenic target. Due to the currently undefined aetiology, rapid response to CST and the selective involvement of the VR or DR, we postulated that chronic HIMRN are nodopathies caused by autoantibodies generated during HIV infection binding to nodal sites, and that the antigenic target in DRG and VR differ.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient recruitment

The study was a prospective descriptive study of a cohort of HIMRN, seen at Inkosi Albert Luthuli Central Hospital, a quaternary referral centre in Durban, South Africa between January 2018, and December 2022 The study was approved by the University of KZN Biomedical Research Ethics Committee (BREC/00005861/2023).

### 2.2 | Inclusion criteria

HIV-infected patients, older than 12 years, with chronic HIMRN were included in the study. Patients were diagnosed with HIV prior to or at the time of diagnosis of the HIMRN. All patients were required to have peripheral nerve dysfunction with or without central disease. Additionally, they needed to fulfil the clinical, electrodiagnostic, and cerebral spinal fluid (CSF) criteria of the European Federation of Neurologic Sciences/Peripheral Nerve Society for CIDP[8] or criteria for VRR or DRG. For the purpose of the study, VRR was defined as: (a) pure motor presentation, (b) progressive disease beyond 3 months (c) VR enhancement on magnetic resonance imaging (MRI).[6] DRG was defined as an immune-mediated pure sensory non-length dependent clinical presentation of longer than 3 months, absent sensory nerve action potentials (SNAPs) on electrophysiology, normal motor studies with or without abnormal blink responses or DR enhancement on MRI.[9]

### 2.3 | Exclusion criteria

Patients were excluded if they did not meet the diagnostic criteria for CIDP, VRR, or DRG, if the clinical presentation was suggestive of GBS, or if secondary causes were identified such as drugs, toxins, paraneoplastic antibodies, diffuse infiltrative lymphocytosis (DILS), connective tissue disease or their HIV status was negative or unknown.

## 3 | INVESTIGATIONS

### 3.1 | Blood and CSF

All patients were screened for HIV with an HIV ELISA test, baseline CD4 counts, and HIV viral load. Other tests included connective tissue screen, ganglioside antibodies (GQ1b, GD1a, GD1b, GT1b, GM1, GM2, and GM3), paraneoplastic antibodies, and serum paraprotein. In addition, CSF IgG index and oligoclonal bands (OBs) were evaluated in some patients.

Patients with optic nerve involvement, in addition to the above were evaluated for aquaporin-4, myelin oligodendrocyte glycoprotein antibodies, and raised serum angiotensin converting enzyme levels for neuromyelitis optica and neurosarcoidosis, respectively. Further tests were conducted to exclude infective or neoplastic causes of a polyradiculopathy as highlighted in Table S3.

### 3.2 | Immune tests

#### 3.2.1 | Live cell-based assay

All patients, prior to commencing therapy, had 10 mL serum and CSF stored at −80 degrees. Serum samples were tested for IgG antibodies directed against nodal (NF186) and paranodal (NF155, CNTN1, and Caspr1) cell adhesion molecules, using a live, cell-based assay (CBA), as previously described.[10–12] In brief, human embryonic kidney 293T cells were transiently transfected with plasmid constructs containing the human cDNA sequences for either CNTN1 and Caspr1, NF155, or NF186. After 24 h, the cells were washed and incubated with patient sera for 1 h at room temperature. Fluorescently tagged secondary and tertiary antibodies against human IgG or human IgG subclasses 1–4 were used to visualise cell membrane binding by an investigator blind to the sample identity.

#### 3.2.2 | Myelin co-cultures and complement activation

Co-cultures were generated using sensory neurons derived from human-induced pluripotent stem cells and primary rat Schwann cells, according to a previously published protocol.[13] Sera (heat inactivated to abolish complement activity and diluted to 1:50) from patients positive for nodal–paranodal antibodies, were assessed for topographical IgG binding, to myelinated co-cultures. For immunolabelling, live co-cultures were incubated with patients' sera for one and 24 hours respectively at 37°C, with or without the addition of normal human serum, as a source of complement, at a dilution of 1:5. Myelin, axons, human IgG were immunostained to assess for myelin or axonal damage and topographical binding of human IgG to neural tissue. Accelerated myelin or axonal injury compared with controls, was an indirect indication of complement activation (Supporting information S1).

### 3.3 | Electrophysiology and radiology and OCT

Standard motor and sensory nerve conduction studies (NCS) were performed on all patients (eight motor nerves including f-wave latencies, six sensory nerves). Electromyography was also performed to assess for axonal loss (Table S1).

Patients with suspected optic neuritis (ON) had optic coherence tomography (OCT), visual-evoked responses (VEP), and MRI brain and orbits performed. Patients with DRG had blink responses, MRI brain, and spine and whole-body positron emission tomography to exclude occult malignancy. Patients with VRR had an MRI spine.

## 4 | TREATMENT PROTOCOLS

Patients were treated with standard therapy for CIDP, which included CST and/or intravenous immunoglobulin (IVIG).[14,15]

If they presented acutely and were clinically suspected of having GBS they were initially treated with IVIG. Patients who had acute onset disease and progressed beyond 4 weeks, were managed as CIDP with CST.[5] All patients with VRR and DRG were treated with steroids, in line with previous experience.[6] Escalation therapy included IVIG, azathioprine (AZA), plasma exchange (PLEX), and Rituximab. This was added at the discretion of the physician, guided by adverse events and response to initial therapy. This is based on standard treatment guidelines used by our unit and international guidelines.[15]

## 5 | STATISTICAL ANALYSIS

Data was entered in Microsoft Excel and analysed using Prism Software. Descriptive statistics such as medians and IQR were used to describe continuous variables and percentages were used to describe categorical variables.

## 6 | RESULTS

Fifty-eight patients were initially recruited for the study. Of these, 30 were excluded as they were HIV-uninfected, one had a history of n-hexane use, two declined HIV testing, and one was diagnosed with tuberculosis polyradiculopathy on CSF polymerase chain reaction.

### 6.1 | Demographics and clinical features at presentation

Twenty-four HIMRN patients were assessed. Table 1 highlights the clinical and demographic features. All participants were of black African ancestry, 13 (54%) were female, median age of 38.5 years (IQR 22–43 years). The cohort consisted of the following clinical categories; 4 (16.7%) had VRR, 5 (21%) had DRG, and 15 (62.3%) had mixed motor and sensory (MSM) CIDP. Among the patients with MSM-CIDP, 4 (27%) patients had ON, and 1 (6.67%) patient had combined central and peripheral demyelination (CCPD). The median Modified Rankin Scale (mRS) scores at presentation were 4. Additional clinical details are included in the supporting information S1.

### 6.2 | Relevant blood and CSF findings

The median CD4 count was 202 cells/μL, IQR 155–212 cells/μL, and viral load (VL) was 40 313 copies/mL (0–90 666 copies/mL). (Table S3). Sixteen (66%) of patients had a polyclonal gammopathy, three patients had positive antinuclear antibody titres of 1:160, speckled pattern, one patient was positive for Ro antibodies and one for Ma2 antibodies. (Table S2). These patients were still included in the study, as the clinical presentation was not related to positive antibody tests. CSF analysis revealed an elevated protein in all patients, median of 1.21 g/L (IQR: 0.98–1.67 g/L) and a modest CSF lymphocytosis, median of 8 cells/μL, IQR (6–16 cells/μL).

Serum and CSF OBs were tested in 11/24 (48%) patients (Table S3).

### 6.3 | Paranodal antibodies

Patient 3 (MSM-CIDP with ON) and patient 16 (DRG) tested positive for NF155 (IgG1, titre 1:200), and patient 21 (VRR) tested positive for NF186 (IgG1, titre: 1:400). Table S2, and Figure 1.

### 6.4 | Myelin co-cultures and complement activation

In the above three patients who tested positive for nodal–paranodal antibodies using live CBA, there was no binding of human IgG to myelin or axons at 1 h and 24 h, respectively. There was also no accelerated myelin damage after the addition of complement (Figure 2).

**TABLE 1** Clinical and demographic features of the HIV-infected cohort with immune-mediated radiculo-neuropathy.

| | Clinical | | | | | | | Investigations and Treatment | | | | | | mRS Scores | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Clinical diagnosis | Onset | Motor or sensory | CN palsy | Autonomic | Pain | Ataxia | CD4 count | NCS (overall impression) | MRI Spine/brain | CSF protein | (+) Nodal/Paranodal antibodies | | Nadir mRS | mRS at 6 months |
| P1 | CIDP | Acute | M & S | X | ✓ | ✓ | ✓ | 122 | Demyelinating | | 1.24 g/L | | CST | 4 | 2 |
| P2 | CIDP | Progressive | M & S | X | X | X | X | 335 | Demyelinating | White matter Dx | 1.28 g/L | | IVIG, CST + AZA | 4 | 2 |
| P3 | CIDP | Progressive | M & S | ✓ ON | ✓ | X | ✓ | 189 | Demyelinating | Normal | 1.22 g/L | NF:155 1:200 (IgG1) | CST + AZA methylprednisone | 4 | 0 |
| P4 | CIDP | Progressive | M & S | X | ✓ | X | ✓ | 288 | Demyelinating | ND | 1.06 g/L | | CST | 3 | 1 |
| P5 | CIDP | Acute Onset, progressive | M & S | ✓ ON | ✓ | X | ✓ | 356 | Demyelinating | Normal | 1.41 g/L | | CST | 3 | 2 |
| P6 | CIDP | Acute | M & S | ✓ ON | X | ✓ | X | 123 | Demyelinating | Optic nerve enhancement | 1.12 g/L | | IVIG, IVI methyl prednisone, CST, AZA | 4 | 3 |
| P7 | CIDP | Progressive | M & S | X | ✓ | ✓ | ✓ | 366 | Demyelinating | ND | 1.76 g/L | | CST | 4 | 1 |
| P8 | CIDP | Progressive | M & S | X | X | ✓ | X | 168 | Demyelinating | ND | 0.99 g/L | | CST | 4 | 3 |
| P9 | CIDP | Acute | M & S | X | X | X | X | 432 | Demyelinating | ND | 0.88 g/L | | CST | 5 | 2 |
| P10 | CIDP | Acute | M & S | X | X | X | X | 132 | Demyelinating | ND | 1.72 g/L | | CST | 5 | 1 |
| P11 | CIDP | Acute | M & S | ✓ ON | X | X | X | 312 | Demyelinating | Optic nerve enhancement | 1.15 g/L | | CST, IV Methyprednisone | 3 | 0 |
| P12 | CIDP | Progressive | M & S | X | X | X | X | 196 | Demyelinating | ND | 0.77 g/L | | CST | 4 | 1 |
| P13 | CIDP | Acute | M & S | X | X | X | X | 122 | Demyelinating | ND | 1.08 g/L | | CST | 4 | 1 |
| P14 | CIDP | Acute | M & S | X | X | X | X | 166 | Demyelinating | ND | 1.33 g/L | | IVIG+CST | 5 | 2 |
| P15 | CIDP | Acute onset Progressive | M & S | X | X | X | X | 196 | Demyelinating | ND | 0.77 g/L | | IVIG + CST | 4 | 1 |
| P16 | DRG | Acute | Sensory only | ✓ TN | ✓ | X | ✓✓✓ | 277 | Absent SNAPs Normal motors studies | Vague DRE | 0.95 g/L | NF:155 1:200 IgG1 | CST/AZA/IVIG ? RTX | 4 | 5 |
| P17 | DRG | Acute | Sensory only | X | X | X | ✓✓✓ | 180 | Absent SNAPs, normal compound muscle action potential (CMAPs) | No DRE | 0.88 g/L | | PE + IVIG+CST | 3 | 4 |
| P18 | DRG | Progressive | Sensory Only | X | ✓ | X | ✓✓ | 223 | Absent SNAPs Abnormal blink | No DRE | 0.61 g/L | | CST + AZA + IVIG | 5 | 4 |
| P19 | DRG | Progressive | Sensory Only | X | ✓ | X | ✓✓ | 214 | Absent SNAPS Abnormal Blink | Vague DRE | 2.13 g/L | | CST + AZA + IVIG | 4 | 4 |
| P20 | DRG | Acute onset progressive | Sensory only | ✓ TN | X | X | ✓✓✓ | 122 | Absent SNAPs Normal motors studies | No cranial nerve enhancement | 1.21 g/L | | IVIG+CST | 4 | 3 |
| P21 | VRR | Progressive | Motor Only | X | X | X | X | 210 | Normal SNAPS, Axonal | VRE | 2.34 g/L | NF186 1:400 (IgG1) | CST | 5 | 1 |
| P22 | VRR | Acute | Motor only | X | X | X | X | 112 | Axonal, normal SNAPs | VRE | 2.23 g/L | | CST | 4 | 1 |
| P23 | VRR | Progressive | Motor only | X | X | X | X | 208 | Normal SNAPs Reduced CMAPs | VRE | 1.66 g/L | | CST | 4 | 2 |
| P24 | VRR | Progressive | Motor only | X | X | X | X | 212 | Axonal, Normal SNAPs | VRE | 2.56 g/L | | CST | 5 | 2 |

Abbreviations: AZA, azathioprine; CST, corticosteroid therapy; DRG, dorsal root ganglionopathy; IVIG, intravenous immunoglobulin; M&S, motor and sensory; mRS, modified Rankin Scale; ND, not done; NF, neurofascin; ON, optic nerve; TN, trigeminal nerve; VRR, ventral root radiculopathy.

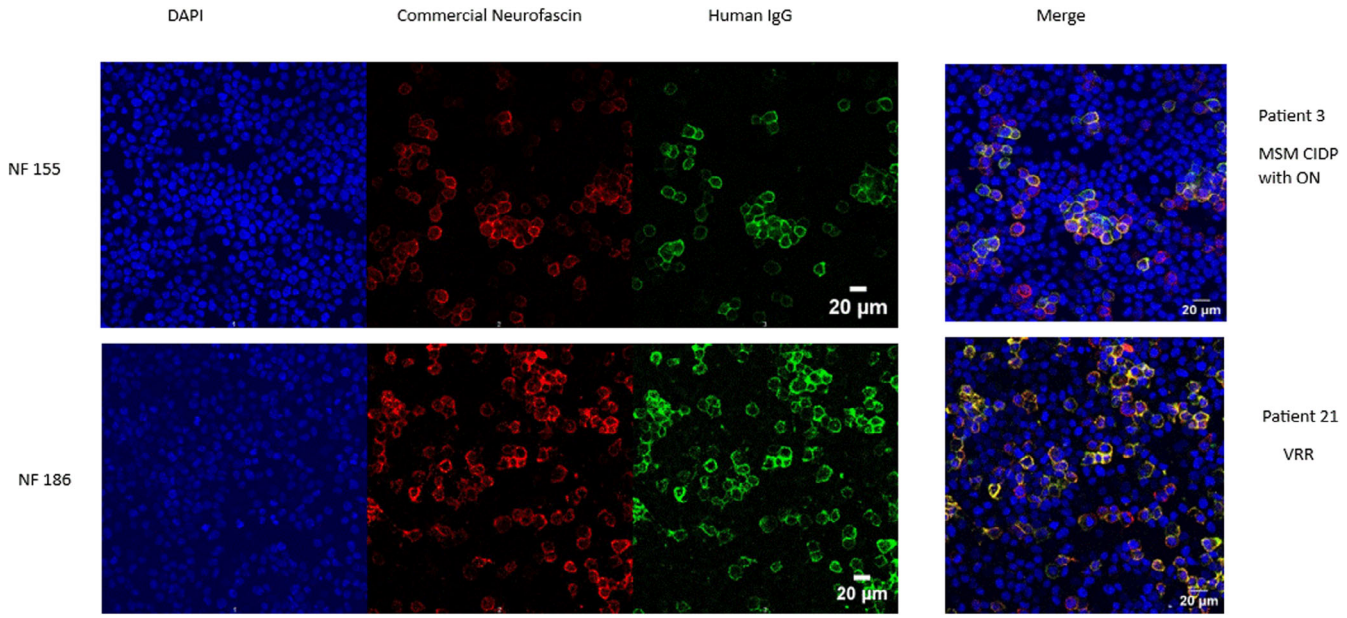


**FIGURE 1** Cell-based assay using fluorescence microscopy. Human embryonic kidney cells are transfected with plasmid vectors encoding the different isoforms of neurofascin, which are expressed as proteins within the cell membrane. Incubation with patient 3 and patient 21 sera allows human anti-neurofascin antibodies (green), if present, to bind to their target antigen. Co-localization (yellow fluorescence) with a commercial neurofascin antibody (red), confirms NF 155 and NF 186 as the target antigen in patients 3 and 21, respectively. MSM = mixed motor and sensory; VRR = ventral root radiculopathy.

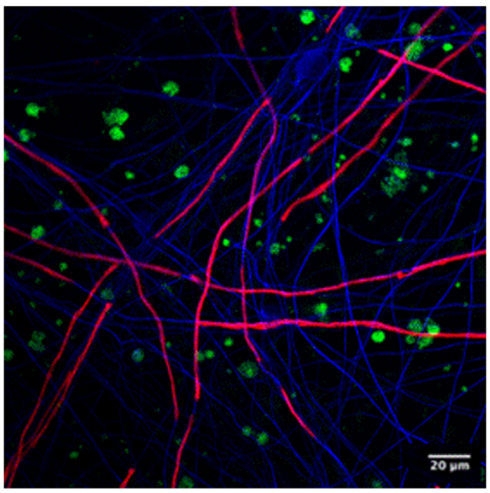


**FIGURE 2** Myelinated co-cultures derived from Hi PSC (axons) and rat Schwann cells (myelin) show no binding of human IgG or complement to neural structures (myelin and axons) up to 24 h after adding sera of patients 3, 16 and 21, respectively and 20% normal human serum as a source of complement. There is also no myelin injury demonstrated during this time frame and no complement activation. Green = human IgG; red = myelin; blue = axons.

## 6.5 | NCS and OCT

Detailed NCS are given in table S1 and visual acuity, VEP and OCT for patients with ON are in Table S4.

## 6.6 | Radiology

The MRI spine showed VR enhancement in all four patients with VRR (Figure 3A). Patient 16 who tested positive for NF155 antibodies showed possible DR enhancement. There was no enhancement of the trigeminal nerve or ganglion in the two patients with clinical trigeminal neuropathy (Supporting information S1). Patient 2 had extensive symmetrical cerebral white matter disease, including the splenium and genu of the corpus callosum (Figure 3B) and two patients had optic nerve enhancement on MRI orbits, one of whom was patient 3 with NF155 positivity.

## 6.7 | Treatment and response to therapy

Patient 21 (VRR), who tested positive for NF 186 responded well to CST which is comparable to the rest of the VRR cohort. Patient 16 (DRG) with NF155 positivity has had poor treatment response and is awaiting escalation therapy with Rituximab and patient 3 (MSM demyelinating neuropathy) with NF155 positivity required AZA in addition to CST due to frequent relapses. Refer to supporting information S1 for treatment and response to therapy in the entire cohort.

The impact of antiretroviral therapy (ART) on recovery was not assessed in this article. Eight (30%) of patients were on ART at the time of presentation, the rest were ART naïve.

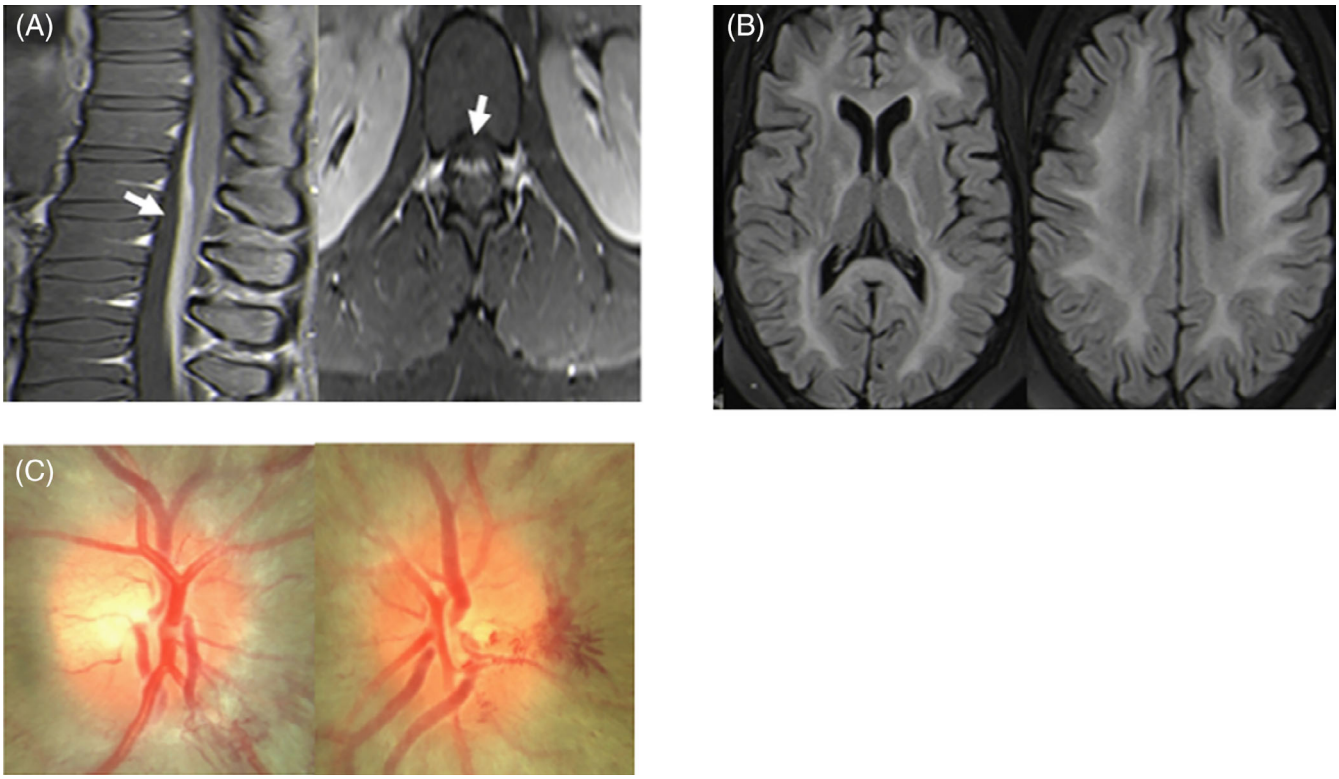


**FIGURE 3** (A) Post-contrast sagittal and axial MRI spinal images of patient 21 showing ventral root enhancement (arrows). (B) Flair axial MRI brain scans of patient 2 showing diffuse symmetrical involvement of the white matter including the corpus callosum. (C) Fundal Images of patient 11 showing swollen discs.

## 7 | DISCUSSION

The main findings of this study are that three (12.5%) of chronic HIMRN were positive for NF IgG1 antibodies. This is comparable to the frequency of nodopathies reported in HIV-uninfected IMRN cohorts.[1]

Thus far, the best characterised clinical profile of nodopathies, relates to NF155 IgG4 antibodies described in peripheral neuropathy, ON, and CCPD.[16–18] Others include pan-NF(IgG1/3), Caspr1, and CNTN1 (IgG4) antibodies.[11,12,19,20] The above are usually refractory to conventional therapy. Less is known about the incidence, prevalence, or relevance of NF IgG1 antibodies in the general population or among HIV-infected patients. Authors have reported NF IgG1 antibodies in a few patients of uncertain clinical significance and NF186 antibodies (IgG subtype undefined) with a heterogenous clinical presentation and good response to CST.[7,21] There has been variable reports of non-IgG4 NF antibodies in AIDP by Devaux et al.[22] and Ng et al.[23] NF IgG2 antibodies have been described in a paediatric cohort.[24] Furthermore, NF186 IgG1 antibodies have been reported in other neurological diseases such as multiple sclerosis, HIV encephalopathy, motor neuron disease, and paraneoplastic syndromes.[25,26]

Despite three patients testing positive for IgG1 NF antibodies, these did not bind to or activate complement in myelinating co-cultures. Classical pathway complement activation requires an antigen–antibody complex, which presumably did not form in vitro. Possible considerations for lack of binding include low antibody titres, low antigenic affinity IgG1 antibodies, antigens in myelin co-cultures being structurally different to antigens present in human HIV-infected neural tissue, presence of different tissue cytokine patterns in pathological nerve or lastly, an unknown co-factor or dual antibodies. As such, the lack of binding of human IgG1 to myelin co-cultures does not exclude a pathogenic role for these antibodies. Several factors such as CSF-restricted OBs, favourable response to PLEX or IVIG,[10] and selective involvement of the VR, DR, and ON may support an antibody-mediated process. However, mechanisms, such as an exclusive cell-mediated response (example, CD8+ T-cell lymphocytosis as in DILS),[27] demyelination related to factors such as cytokines example tumor necrosis factor alpha[28] or viral induced as in progressive multifocal leukoencephalopathy, remain a possibility, although less likely.[29]

This study has several limitations, which include small sample size; hence, reliable conclusions cannot be made regarding differences in antibodies in the different phenotypes or response to therapy. Others include limited testing for other known or unidentified nodal–paranodal antibodies, use of myelin derived from rat Schwann cells, not controlling for stages of HIV infection, or effects of ART, limited longitudinal follow-up of patients and laboratory error.

Nevertheless, the above serves as a platform for future larger studies using myelin derived from Hi PCS, incubated with patients serum containing 'live' HIV virus and other co-factors. This will create

an 'inflammatory' environment, which may alter the expression or configuration of antigens enabling binding. Additionally, human myelin cultures will overcome species differences in antigen expression and be more reflective of the disease model in its 'live, native form'. Other potential studies include use of human VR, DRG, oligodendrocytes, or even ON cultures to define antigenicity of these sites regardless of HIV status or techniques such as gene sequencing, PCR, or immunoblot of protein lysates derived from different neural tissue.[30]

## 8 | CONCLUSION

The study, although small, is the first study in an HIV-infected cohort from Africa describing nodal–paranodal antibodies at a similar frequency to European studies. However, interpretation of results in the context of HIV, especially with low titre, IgG1 antibodies is challenging as low-affinity antibodies may occur as an epiphenomenon in HIV. The study provides direction for future research, in terms of establishing pathogenicity of the antibodies by using a myelin culture model that is more reflective of the HIV-infected cohort. It also highlights the importance of testing for IgG subclasses and developing panels of antibodies that select for specific phenotypes. This will provide direction for the establishment of targeted immunotherapy.

### AUTHOR CONTRIBUTIONS

KM designed and conceived the study. All patient data and samples were contributed by KM. Patient samples analysed by VM and JF using live CBA and myelinated co-cultures. KM wrote the original manuscript. SR revised the work critically for important intellectual content and supervised the laboratory work. VBP, AAM and PLAB edited and reviewed the manuscript. All authors approved the final manuscript.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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