Combined central and peripheral demyelination in two siblings, immune mediated or genetic?

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ABSTRACT

We report unusual cases of combined central and peripheral demyelination in two siblings related to pregnancy, each presenting with progressive tetraparesis and cranial nerve palsies. The elder sister had a relapsing–remitting course with optic nerve dysfunction and died during a relapse from respiratory insufficiency. The younger sister presented with disorientation and acute-onset limb and facial weakness. She responded well to corticosteroid therapy. Their clinical presentation, response to immunomodulatory therapy, nerve conduction studies, cerebrospinal fluid and histology supported an acquired demyelinating cause. Whole-exome sequencing identified variants in two genes not previously linked to this clinical phenotype. Serological tests for antibody-mediated demyelination were negative. Despite the undefined pathogenesis, these cases provide a platform to explore the confluence of genetic, immune and environmental factors in the context of acquired demyelination. We discuss the differential diagnosis and a diagnostic approach to such cases from the perspectives of neuroimmunology and neurogenetics.

CASE 1

A woman in her late twenties presented with headaches, asymmetrical lower limb weakness and paraesthesias, 1 month post partum. The weakness had progressed over 3 weeks to include the upper limbs. One month later, she had developed poor vision. On examination, she had bilateral impaired visual acuity (right eye: counting fingers; left eye: 20/100), central scotomas, poorly reactive pupils and bilaterally swollen optic discs (online supplemental figure 1) Her ulnar, common peroneal and sural nerves were clinically thickened. All four limbs were flaccid, with MRC grade 4 strength in distal muscles and grade 4 proximally, with the left affected more than the right. She was areflexic and the plantar responses were equivocal. She had a symmetrical glove and stocking sensory impairment to pin prick and light touch to the knees and elbows, respectively, and joint-position sense was impaired at the toes and fingers. Optical coherence tomography (OCT) confirmed bilateral peripapillary thickened retinal nerve fiber layer, RE:293 μm, LE:191 μm. Visual evoked potentials showed prolonged P100 latencies, right eye: P138 ms, left eye: P128 ms. Nerve conduction studies confirmed demyelination and cerebrospinal fluid (CSF) were consistent with an inflammatory disorder (online supplemental figure 1, table 1 and table 2A,B).

Having excluded other clinically relevant secondary causes of demyelination (online supplemental table 2A,B), she was managed as having chronic inflammatory demyelinating polyneuropathy (CIDP) with a 5-day course of intravenous immunoglobulin (IVIG) at 1 month following symptom onset. Despite her vision improving to near normal over the following weeks, her tetraparesis improved only minimally over the subsequent 8 months while maintained on azathioprine 150 mg daily and oral corticosteroids. She was therefore started on mycophenolate mofetil 1.5 g two times a day at 12 months and improved over the subsequent year, such that she could walk with support, hold objects and feed herself. Approximately 2 years into her illness (figure 1) she relapsed, with tetraparesis and visual loss, having defaulted treatment for the 6 months before. Examination confirmed, poor

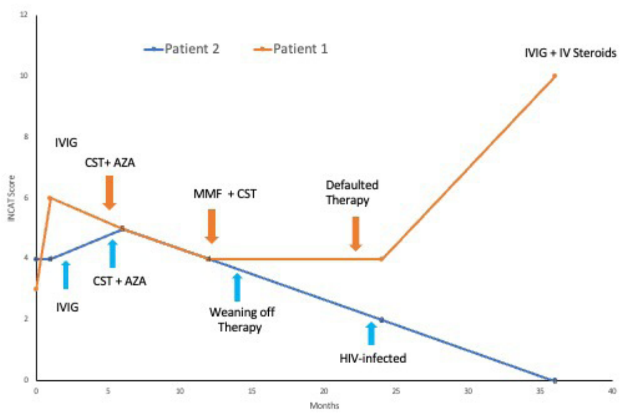

Figure 1 Timeline of disease progression, inflammatory neuropathy cause and treatment scores and therapy administered. AZA, azathioprine; CST, corticosteroid therapy; IVIG, intravenous immunoglobulin.

visual acuity (right eye: nil light perception, left eye: counting fingers), bilateral optic atrophy, paraplegia in the lower limbs, MRC grade 1–2 strength in the upper limbs, and markedly impaired joint-position sense, light touch and pin prick up to the knees in the lower limbs and elbows in the upper limbs. MR scan of the brain (figure 2) confirmed central demyelination. An MR scan of the spine was not done. She continued to deteriorate despite a repeat course of IVIG and intravenous methylprednisone. She died from respiratory failure due to diaphragmatic weakness arising from a phrenic nerve neuropathy, while awaiting an intensive care unit bed for ventilatory support. Postmortem histology confirmed demyelination of the cerebral white matter and peripheral nerves (figure 3).

CASE 2

Her younger sister, in her early 20s, with the same biological parents, presented with acute facial weakness, 2 weeks post partum. Her weakness progressed to involve upper limbs and lower limbs within the subsequent 2 weeks. She was also disorientated to time and place. She had bifacial weakness, flaccid, areflexic tetraparesis with distal strength of MRC grade 4− in both the upper and lower limbs, and glove and stocking sensory impairment to pin prick, light touch and joint position sense. Despite normal visual acuity, the P100 latencies were bilaterally prolonged: right eye: 118 ms, left eye: 120 ms and OCT was normal.

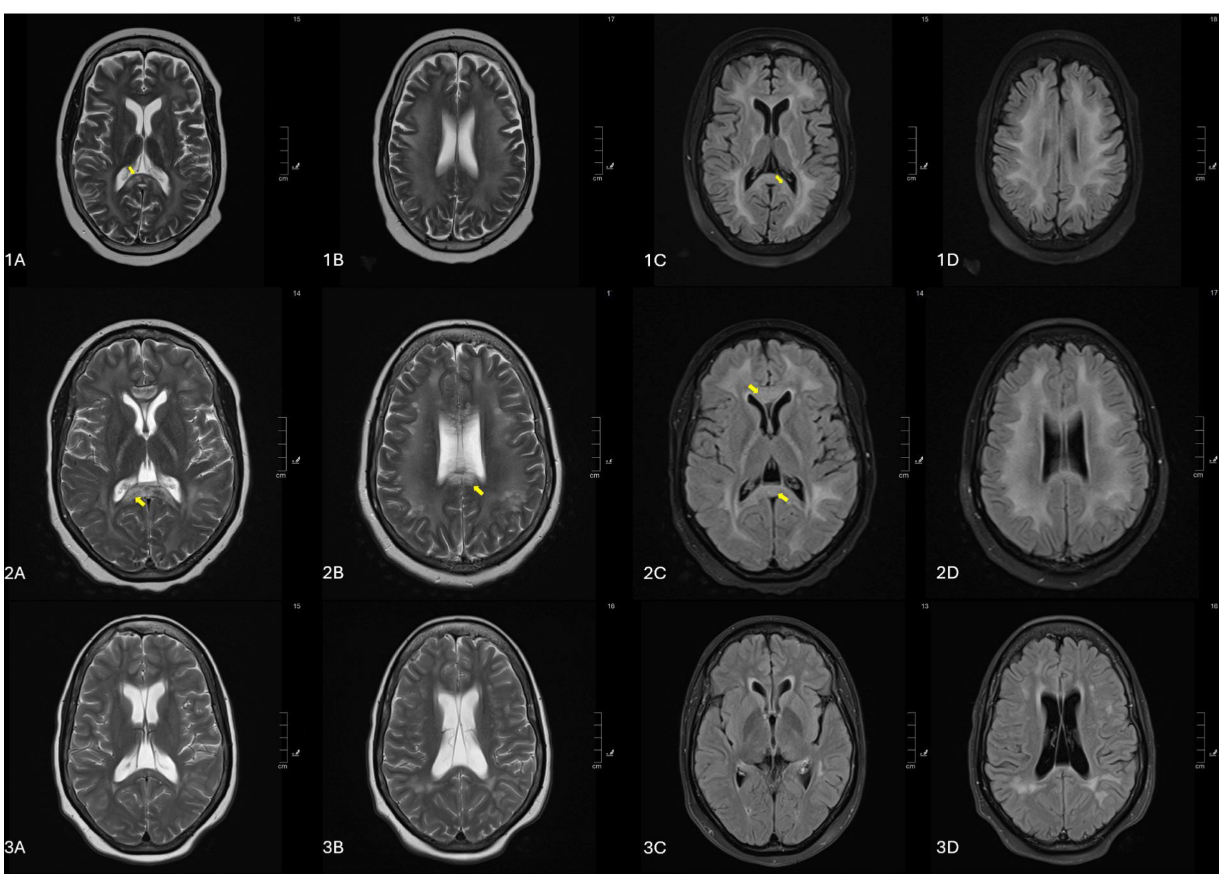

Figure 2 MR images of the brain of patient 1 (image 1) and patient 2 (image 2) during a relapse: axial T2 (A, B) and T2 fluid-attenuated inversion recovery (C, D) images show diffuse white matter hyperintensities involving the bilateral hemispheres and the splenium and genu of the corpus callosum (arrows). Image 3 (patient 2 post treatment): axial T2 (A, B) and T2 fluid-attenuated inversion recovery (C, D) images show significant resolution of previous white matter hyperintensities seen in image 2.

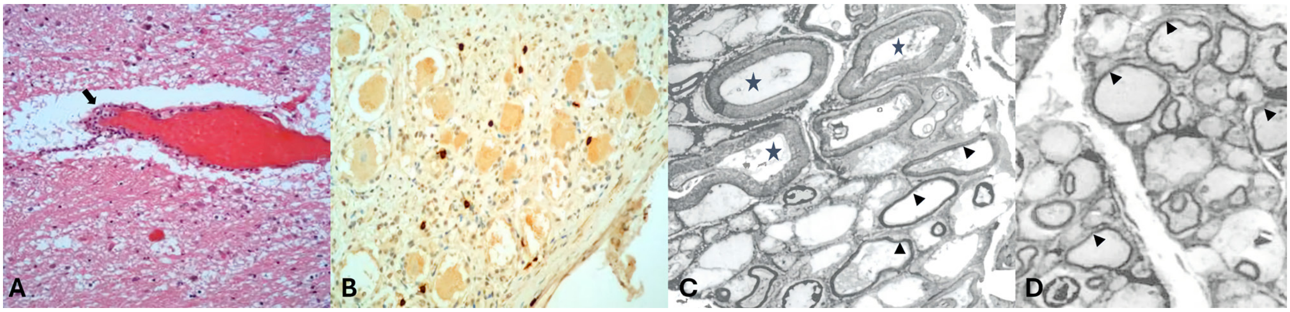

Figure 3 Postmortem histology of brain and peripheral nerves. (A) H&E staining of sections of the brain demonstrating spongiosis consistent with perivascular demyelination and perivascular inflammatory infiltrates. (B) Dual immunohistochemical staining of phrenic nerve: infiltration of the nerve by CD3 T lymphocytes and CD8 macrophages. (C, D) Electron microscopy of the phrenic nerve and brachial plexus demonstrating large axons with abnormally thin myelin (arrow heads, G ratio >0.6), consistent with demyelination. Axons surrounded by normal myelin (stars, normal G ratio).

Her nerve conduction studies were consistent with demyelination (online supplemental table 1). Initially, she was managed as having an acute inflammatory demyelinating polyneuropathy with IVIG, and later started on corticosteroid therapy (60 mg daily) and azathioprine 100 mg daily as she continued to progress beyond 12 weeks (figure 1). This is the standard protocol in our unit for CIDP and is consistent with international guidelines. An MR scan of brain was performed due to the subclinical visual involvement, disorientation and her sister having presented with central disease, figure 2, images 2 and 3.

Although initially HIV-uninfected, 2 years later, she tested HIV-positive with a CD4 count of 333 cells/mm^3 and a viral load of 94 712 copies/mL. She was started on antiretroviral therapy.

Her weakness and sensory symptoms improved during the subsequent 2 years while maintained on 10 mg prednisone and 100 mg azathioprine daily with no documented adverse effects. Currently, she is well with full functional recovery and is being tapered off immunosuppressant therapy.

Figure 1 reflects the timeline of disease progression, inflammatory neuropathy cause and treatment disability scores and therapy for both patients.

Both sisters had lived together, with no exposure to toxins, or recreational drugs and were unaware of similar clinical presentations in the neighbourhood or among family members.

INVESTIGATIONS

Blood and CSF results

Serological investigations in both sisters were negative for antibodies against ganglioside, lactosylceramide, myelin-oligodendrocyte glycoprotein (MOG), myelin-associated glycoprotein (MAG), aquaporin-4 (AQP-4), paraneoplastic and nodal-paranodal antigen, which included neurofascin (NF)155, NF186, Contactin-1 and CaspR-1. Human-induced pluripotent stem cell myelin co-culture screens were negative (online supplemental table 2A,B)

Serum ACE was normal, with no identified paraprotein and the connective tissue screen was negative. Common infections were excluded. A primary, biochemically defined metabolic disorder and an inherited leukodystrophy were clinically unlikely (box 1). This was supported by normal leucocyte arylsulfatase A activity, very long-chain fatty acids and serum lactate.

Whole-exome sequencing, carried out as previously described,[1] identified a missense variant in *PPFIA4* and a nonsense mutation in *CHCHD10*. Although not previously linked with the phenotype present in these patients, both variants were predicted to be functionally deleterious by their corresponding in-silico scores. Further segregation analysis as well as functional assessment would be necessary to assess their contribution to these phenotypes. There were no identified mutations in genes linked to leukodystrophy, mitochondrial cytopathy, metabolic disorders or inherited neuropathy.

Both patients had raised CSF proteins (0.97 g/L and 1.28 g/L, respectively); patient 2 had eight lymphocytes in the CSF while patient 1 had no cells. Both had positive CSF oligoclonal bands (type 2 pattern with oligoclonal IgG bands in the CSF but not in serum, suggesting intrathecal IgG synthesis). Cytology identified no malignant cells.

Radiology and electrophysiology

MR scan of brain and electrophysiology were consistent with demyelination in both patients. In patient 2, repeat nerve conduction studies and MR scan of brain showed recovery (figure 2, and online supplemental table 1).

DISCUSSION

CIDP is the most common chronic autoimmune neuropathy with diverse clinical presentations, including central demyelination. In these cases,

Box 1 Differential diagnosis of CCPD

Acquired
Immune mediated:
- CIDP and its variants
- GBS and its variants (Bickerstaff's encephalitis)
- Neurosarcoidosis
- Less commonly: MS, NMO, MOGAD

Malignancy:
- Paraneoplastic disorders
- Neurolymphomatosis

Drugs and toxins:
- Toluene, N-hexane
- Immune checkpoint inhibitors
- Tacrolimus
- Anti-TNF therapy

Vitamin E deficiency: malabsorption syndromes
Infections:
- Leprosy
- HTLV-1

#Inherited:
Mitochondrial disorders:
- NARP
- Pyruvate dehydrogenase deficiency syndromes
- MNGIE

Storage diseases:
- Refsum's disease
- Sulfatide lipidosis

Neuropathies:
- CMT (GJB1 mutations)

Leukodystrophy:
- Metachromatic leukodystrophy,
- Krabbe leukodystrophy

Others:
- Abetalipoproteinaemia
- Familial amyloidosis

***Genetic-autoinflammatory disorders**

CCPD, combined central and peripheral demyelination; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; MOGAD, myelin oligodendrocyte glycoprotein-associated disease; MNGIE, mitochondrial neurogastrointestinal encephalopathy syndrome; MS, multiple sclerosis; NARP, neuropathy, ataxia, retinitis pigmentosa; NMO, neuromyelitis optica. [#]Progressive signs, symptoms present early in life, and usually are not corticosteroid-responsive. [*]Signs of systemic disease (fever, skin rash, polyarthralgia) and multisystem involvement.

lesions may resemble those of acute disseminated encephalomyelitis, encephalo-myeloradiculoneuropathy, myelin oligodendrocyte antibody-associated disorders, neuromyelitis optica and multiple sclerosis. CIDP with central demyelination has been described using many terms, the most common being combined central and peripheral demyelination (CCPD). Other inherited differential diagnoses include metabolic disorders such as metachromatic leukodystrophy, Refsum's disease, mitochondrial cytopathy and genetic disorders such as Charcot-Marie-Tooth disease with *GJB1*(gap junction beta-1 protein) mutations listed in box 1.

The immunopathology of CCPD is unknown. Current literature supports an antibody-mediated process targeting common central and peripheral myelin or macrophage-induced demyelination. NF155 antibodies have been described mainly in cases from Japan and fewer from Europe.[2] More recently, glycolipid lactosylceramide antibodies were identified in two Japanese patients.[3] In a larger case series from Europe, no identifiable antibodies were reported.[4] Other antibodies described in this condition include AQP-4, MAG, GQ1b, MOG and paraneoplastic antibodies, which were negative in the patients described here. Patients with CCPD usually respond to conventional therapy used in CIDP, which includes corticosteroids, plasma exchange, IVIG or B cell-depleting therapy such as rituximab in the case of NF155 associated CCPD, or treatment of the underlying malignancy in the case of the paraneoplastic manifestation of this condition.[5–7]

Unusual findings in both cases were that of symmetrical cerebral white matter involvement and demyelination of the corpus callosum. This may occur with toxins (benzene or toluene) or inherited disorders, which were less likely in these patients as they were corticosteroid responsive and had no history of toxin exposure. Useful bedside features favouring acquired demyelination, although not absolute, include: acute-onset and rapid disease progression, positive sensory symptoms, asymmetrical clinical signs, presence of CSF-restricted oligoclonal bands, asymmetrical temporal dispersion and blocks on nerve conduction studies. Pregnancy may be an external precipitating factor. The most convincing evidence for acquired demyelination was the profound response to corticosteroid therapy in patient 2, and relapse of disease when stopping corticosteroid therapy in patient 1. It can be challenging in practice to differentiate acquired from inherited demyelination as they may have similar presentations and there is no absolute gold standard to distinguish one from the other (or their coexistence) except for genetic testing.

The siblingship of these cases was an unusual presentation. To date, there are no described mutations in this condition. The limited genetic information that exists in demyelination is from patients with typical CIDP. This includes mutations in *SH2D2A*, M3 allele of alpha-1 and HLA associations with *HLA-DR2, HLA-DR3, HLA-DQ2* and *HLA-DRB15* associated with anti-NF155 nodopathy.[1 8] There are case reports of genetic neuropathies coexisting with CIDP or having a

CIDP-like presentation, which makes the diagnosis and management challenging. This includes pathogenic variants in *CMT 4C, CMT 1B,* metachromatic leukodystrophy and mitochondrial disorders.[9 10] Genetic autoinflammatory disorders and other acquired disorders such as vitamin E deficiency were less likely in the patients described here as they did not have features of systemic inflammation, malabsorption syndromes or multisystem disease.[11]

Pregnancy-related factors include maternal T cell responses that acquire a transient state of tolerance for fetal H2 antigens and microchimerism, which can persist for decades. McCombe *et al* described CIDP in nine women related to pregnancy.[12] The coexistence of HIV infection in case 2 may have been coincidental or may have resulted in a dampened immune response, less-aggressive disease and a quicker response to therapy as previously reported in other CIDP cases from South Africa.[13]

Limitations include not using a human-derived myelin culture model of oligodendrocytes and Schwann cells in their native environment to screen for common novel antigens. Identification of the causative genes in autoimmunity and tolerance may require whole-genome sequencing or long-read sequencing technologies to cover for non-coding and structural genetic variations. Moreover, screening additional family members, for example, the elder sister (not done), as well as carrying out Sanger validation studies in the whole family would be important to provide more genetic information on the identified variants.

The cases highlight the need for multicentre genome-wide association studies. This will allow for better understanding of single nucleotide polymorphisms in different populations, and in complex diseases such as immune mediated demyelination, which are likely due to an interplay between multiple genes and various environmental factors such as pregnancy.

However, in the context of this uncommon disorder, antibodies against NF155, lactosylceremide, AQP-4, GQ1B, MOG, CV2/CRMP5 should be excluded, despite most reported cases being antibody negative. Future discovery of novel pathogenetic antibodies will direct therapy, for example, B cell-depleting therapy, if anti-NF155 positive.

Box 2 Antibodies associated with CCPD

- Neurofascin-155
- Lactosylceremide
- GQ1B ganglioside
- Myelin-oligodendrocyte glycoprotein
- Aquaporin-4
- Collapsin-response mediator protein 5 (CV2/CRMP5)
- #Myelin-associated glycoprotein

#=rare association.

Key points

- Combined central and peripheral demyelination is uncommon and has a wide differential diagnosis.
- Acquired forms are associated with various antibodies (box 2) but usually the antibody remains undefined or the condition results from cell-mediated demyelination.
- Most patients respond to a range of conventional immunosuppressive therapies, including corticosteroids, plasma exchange or IVIG; however, patients with NF155 antibodies usually respond more specifically to B cell-depleting therapy such as rituximab.
- Inherited or genetic causes of combined central and peripheral demyelination present early in life, are progressive and do not usually respond to immunotherapy.

Further reading

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Competing interests None declared.

Patient consent for publication Consent obtained from next of kin.

Ethics approval The study was approved by the University of KZN Biomedical Research Ethics Committee (BREC/00005861/2023).

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