Anti-Neurofascin IgG2 Associated Paediatric Autoimmune Nodopathy

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ABSTRACT

In this case series of four paediatric patients we present the first described cases of immunotherapy responsive autoimmune nodopathy with IgG2 anti-neurofascin antibodies. In 3/4 cases the anti-neurofascin antibodies were predominantly of the IgG2 subclass, a novel finding in comparison to previously described adult cases where IgG4 and/or IgG1/3 have typically been described. One patient had low signal for IgG2 with predominant IgG1 and IgG4 antibodies, a pattern commonly seen in adult patients. Two patients have antibodies targeting all three neurofascin isoforms (155, 186 and 140), whereas antibodies in the sera from the third only targeted the nodal isoforms 186 and 140, and the fourth patient only NF155. The three patients with IgG2 predominant antibodies appear to be responsive to IVIG to varying degrees thus far whereas the patient with IgG1/4 antibodies had poor response to IVIG but good response to steroids. Although the full clinical significance of IgG2 predominant anti-neurofascin antibodies in the context of childhood polyneuropathy remains unclear, emerging evidence of serological-phenotypic correlation may inform prognostication and therapeutic decision making, warranting further study into this area.

SHORTENED TITLE

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WHAT THIS PAPER ADDS

- These cases represent a novel finding of paediatric immunotherapy-responsive neuropathies associated with anti-neurofascin antibodies predominantly of the IgG2 subclass in 3/4 patients.
- Identification of antibodies and understanding their phenotypic relevance could predict response to treatment and guide therapeutic decision making in children

INTRODUCTION

Auto-antibodies directed against specialised peripheral nerve regions have recently been detected in some patients with acquired neuropathies. Neurofascin (NF) 186/140 (NF186/140) at the node of Ranvier; and NF155, Contactin-1 (CNTN1), and Contactin-associated protein-1 (CASPR1) at flanking paranodes have all emerged as specific targets. Such antibodies are associated with disruption of saltatory conduction and specific clinical phenotypes and response to treatment. [1, 2] Although patients with these antibodies may initially be diagnosed with, and meet diagnostic criteria for, Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP), they are better considered as comprising distinct diseases, now termed *autoimmune nodopathies.* [3]. *Nodo-paranodopathy,* also encompassing forms of GBS with ganglioside-antibody mediated nodal conduction failure, has also previously been proposed as an umbrella term to describe these disorders. [4]

In previous studies, nodal/paranodal antibodies were most often predominantly of the IgG4 subclass, although IgG1 or IgG3 predominant patients have also been reported. The clinical significance of this is not yet fully clear; however evolving evidence of phenotypic correlation may help prognosticate disease course and guide treatment. [5]

The diagnostic laboratory in Oxford, UK, introduced screening for nodal/paranodal antibodies in August 2017, testing serum samples from 1301 patients (as of December 2021) using a live, transiently-transfected cell based assay. [6] 7/38 (18%) paediatric patients (aged ≤18 years) tested positive. Adults with nodal/paranodal antibodies show distinct clinical features compared to those with seronegative GBS or CIDP, and frequently respond poorly to IVIG. Table 1 compares the clinical features of the seven nodal/paranodal seropositive paediatric patients, collected via a standardised request form, to the 13 seronegative controls for whom data were available. There were no significant differences between these groups, with a trend towards improved IVIG responses in the seropositive group. Of the 7 seropositive paediatric patients, one with CNTN1 antibodies was included in a previous series [7] and one 17-year-old had NF155 monospecific IgG4 antibodies. Three patients were positive for NF186/140 antibodies, with two also cross-reacting with NF155, a pattern previously termed “pan-neurofascin”. [8]

In contrast to previously described cases, here we present 3 patients in whom IgG2 anti-neurofascin antibodies were the sole or predominant IgG subclass in the context of a childhood polyneuropathy, the first known report of this clinical presentation associated with neurofascin-specific antibodies of the IgG2 subclass; and compare against a patient with predominant IgG1/4 antibodies, a pattern more commonly seen in adult patients.

Table 1: Comparison of paediatric nodal/paranodal seropositive patients compared to seronegative controls.

CASE REPORTS

CASE 1

A 5-year-old male presented with progressive ataxia, lower limb weakness and areflexia 10 days following a tick bite. MRI brain and spine showed bilateral oculomotor nerve, cervical nerve root, and cauda equina nerve root enhancement. Cerebrospinal fluid (CSF) protein was elevated (2.3g/L).

Treatment with intravenous ceftriaxone and intravenous immunoglobulin (IVIG) (2g/kg over 5 days; commencing Day 2 of admission), for the differential diagnoses of neuroborreliosis and GBS respectively, was given with good clinical response (able to walk again with normal fine motor skills after 5 days). Borrelia PCR was negative. Nerve conduction studies (NCS) 5 weeks post presentation were supportive of an acquired inflammatory demyelinating polyneuropathy. The patient followed a relapsing-remitting course consistent with CIDP and was treated with two further courses of IVIG 5 and 11 weeks following initial presentation; the clinical response to repeat courses of IVIG being reduced compared to initial presentation. Repeat MRI showed no significant change; repeat CSF studies showed persistently elevated protein (4.7g/L). Further investigation revealed serum pan-neurofascin antibodies predominantly of the IgG2 subclass targeting NF155 and NF186/140 (Figure 1). He made gradual slow recovery whilst receiving four further doses of IVIG every 3 weeks and then every 4 weeks for a further 6 months.

CASE 2

A 5-year-old male presented with progressive lower limb weakness and areflexia over 5 weeks. Upon presentation his proximal power was 4/5 in the upper limbs and 3/5 in the lower limbs, with a positive Gower's sign. MRI brain and spine were normal, with initial NCS unremarkable aside from absent F-wave responses. CSF protein was 0.52g/L. He was initially treated as having Guillain-Barre syndrome, with IVIG commenced within one month of symptoms, but his clinical evolution led to this being reclassified as CIDP. He was poorly tolerant of prednisolone and mycophenolate mofetil. Rituximab produced an initial response but was discontinued due to significant adverse reaction to further infusions. Repeat NCS 4 years into disease course demonstrated a multifocal demyelinating sensory and motor neuropathy meeting diagnostic criteria for CIDP. IgG2 predominant pan-neurofascin antibodies were found to be positive almost 5 years following initial presentation. He continues on regular 3-weekly IVIG at 5 years, with his examination demonstrating normal power (5/5) throughout but ongoing areflexia, with relapse of symptoms in the absence of IVIG infusions.

CASE 3

A male patient aged 2 years 8 months presented with profound ascending weakness evolving over 2-4 months, developing absence of anti-gravity movements of the lower limbs, marked weakness of his upper limbs, poor truncal stability and evidence of bulbar palsy. MRI demonstrated enhancement of the cauda equina nerve roots. CSF protein

was 1.05g/L. NCS confirmed abnormal sensory and motor responses consistent with a demyelinating peripheral polyneuropathy. Further investigation revealed NF186/140 antibodies (IgG2 predominant). The patient exhibited excellent clinical improvement following IVIG with improvement in bulbar function and upper limb function returning to normal. Following a relapse at 3 months, IVIG was again given but a significant allergic reaction resulted in conversion to monthly intravenous methylprednisolone with good improvement in motor function until 8 months after initial presentation when he developed further upper limb weakness. Rituximab was declined by the family; treatment was complicated by a femoral fracture requiring rehabilitation although motor improvements were subsequently seen without further treatment.

CASE 4

A 2 year 3 month old female patient presented with 6 week history of progressive lower limb weakness. MRI brain and spine were normal and CSF protein 1.9g/L. A diagnosis of GBS was made and treated with IVIG 2g/kg. Over the next 4 weeks weakness progressed to complete loss of ability to walk and mild shoulder girdle weakness. NCS showed abnormal sensory and motor responses with absent/prolonged F-waves consistent with a demyelinating polyneuroradiculopathy. Treatment with prednisolone (initially high dose and then weaning for 8 weeks) resulted in significant improvement with independent mobility achieved within two weeks but ongoing proximal hip weakness. A further course of prednisolone was not beneficial. CIDP was suspected and repeat MRI spine 12 months after onset showed mild cauda equina root enhancement with CSF protein 0.8g/L. NF155 IgG was 1:800; this was predominantly IgG4 and IgG1 with low signal for IgG2. Pulsed monthly dexamethasone for 3 months resulted in complete resolution and the patient remains relapse-free after a further 2 months.

Appendix 1 summarises the clinical presentations of the four patients.

CELL-BASED ASSAY

Figure 1 illustrates the serum antibodies targeting the NF-antibodies in the four patients using a live, cell-based assay.

Figure 1 – Cell-based assay using fluorescence microscopy (x40 magnification)

DISCUSSION

CIDP is rare within the paediatric population; the crude incidence estimated to be 0.06 per 100,000 person years in patients <15 years (versus 0.54/100,000 in patients ≥15years), with a male predominance differing from the female preponderance of many

other immune disorders. [9] Latest CIDP guidelines consider patients with nodal/paranodal antibodies to have a distinct disease, termed autoimmune nodopathy. [3]

Several phenotypes are recognised and improved correlation with serological findings may inform prognosis and therapeutic management. Anti-NF155 antibodies (predominantly of the IgG4 subclass) have been detected in up to 18% of patients otherwise meeting diagnostic criteria for CIDP [10, 11] and are associated with a more aggressive, motor-dominant phenotype, with younger age of onset; ataxia and tremor; higher CSF protein levels; [10, 11] and marked symmetrical hypertrophy of the cervical and lumbosacral spinal roots and plexuses. [10] Cases poorly responsive to IVIG have improved following treatment with Rituximab, an anti-CD20 monoclonal antibody. [11, 12] Recently, a severe phenotype comprising a rapidly progressive tetraplegia in eight adult patients with both NF155 and NF186 antibodies of the IgG1 subtype has been described, with cranial, autonomic and respiratory dysfunction very common and nephrotic syndrome an occasional feature. [8] They were poorly responsive to standard immunotherapy (IVIG, steroids and/or plasmapheresis); 4 died from respiratory failure and the 4 surviving patients showed progressive improvement following rituximab. A further study identified 3 adult patients with IgG3 pan-neurofascin (NF155/186/140) antibodies presenting with a fulminant course comprising tetraplegia and severe cranial nerve involvement (2 diagnosed with CIDP and 1 with GBS). [13] In addition, an NF155 antibody-positive patient with IgG4 and IgG2 antibodies (IgG4>IgG2) had a more severe disease course than that of another IgG4 predominant anti-NF155 positive patient in the same cohort. Another study identified a subset of patients (5/246; 2%) diagnosed with CIDP with anti-NF antibodies, predominantly of IgG4/IgG3 subclasses, associated with sub-acute onset ataxia and cranial nerve involvement. [14] This cohort included one paediatric patient aged 17 months at onset with excellent response to IVIG; the remaining adult patients were documented to have concomitant autoimmune disorders at presentation.

Autoimmune nodopathies may be more common in paediatric patients than is currently appreciated with variable response to IVIG as found in adults. A review of 54 retrospectively screened paediatric patients with diagnoses of GBS or CIDP found 5/12 (41.7%) 'CIDP' patients were positive for IgG4 predominant nodal/paranodal antibodies (2 pan-neurofascin (NF155/186/140), 1 NF155 and 2 CNTN1) although no GBS patients were positive. [7] Of note all 5 seropositive patients presented with ataxia, compared to 1/7 seronegative CIDP patients, suggesting this may be the predominant clinical feature of IgG4 related autoimmune nodopathies in children. One patient was initially diagnosed with GBS (as in Cases 1, 2 and 4) with diagnosis subsequently reclassified, whilst the other patients had an insidious onset and progression of disease over months or years; highlighting the presence of these antibodies as potentially predictive of a chronic course. The two patients with pan-neurofascin antibodies showed a partial response to IVIG and received steroids, with one patient receiving concomitant plasma exchange and the other mycophenolate mofetil. Both recovered slowly over up to 4 years. The 3 remaining patients were unresponsive to IVIG, with marked improvement noted following the administration of rituximab. [7] These findings would support the testing of nodal/paranodal antibodies in paediatric patients with suspected CIDP and an atypical or prolonged course, ataxia and/or tremor.

The reason for, and full clinical significance of, the finding of IgG2 predominant antibodies in contrast to IgG4/3/1 predominant cases in adults, is as yet unclear. In accepted models of B-cell development, naïve B-cells encounter antigen in germinal centre reactions. During this process, somatic hypermutation changes the antibody binding kinetics of the B-cell receptor ("affinity maturation"), which may in some cases generate autoreactivity *de novo*. Further, the process of class switch recombination alters the Ig isotype from IgM/D to IgG, IgA or IgE. Further sequential IgG (sub)class switching is classically thought to evolve from IgG3 to IgG1 to IgG2 and then IgG4. Adults typically have higher levels of somatic hypermutation and more frequent utilisation of downstream subclasses, including IgG2, which is likely to reflect repeated or prolonged antigen exposure. It is therefore surprising that whilst adults frequently have IgG1/3 pan-neurofascin antibodies [8], in this paediatric series all pan-neurofascin and NF186 antibodies were of the IgG2 subclass. This may reflect differences in exposure to infection or T-cell regulation of class-switching between adults and children. Both IgG2 and IgG4 have limited scope for activating complement and engaging cellular effectors, and have previously been suggested to have a regulatory, anti-inflammatory function. This may be relevant to the apparently better outcomes to IVIG in IgG2 versus IgG1 pan-neurofascin antibodies.

In summary, in our three IgG2 predominant patients, symptoms occurred in a younger age group than previously reported IgG1/3 or IgG4 predominant NF-antibody associated neuropathies, although Case 4 highlights IgG1/4 predominant patients can present at this age and appeared to respond well to steroids. All three IgG2 predominant patients appear to be responsive to IVIG to varying degrees thus far suggesting there is potential for targeted immunotherapy based upon serological-phenotypic correlation in nodal/paranodal antibody-positive neuropathies, and further research into this area is certainly warranted.

ETHICAL STATEMENT

Informed consent was obtained from the families of the patients involved in this case series.

COMPETING INTERESTS

Nil competing interests declared.

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Nil declared.

AUTHOR CONTRIBUTIONS

RH collected case details and prepared the manuscript with comments and review from all authors.
MA assisted manuscript preparation and literature review and edited the manuscript for final submission
JtWN, **GBL** and **SRa** provided case details and critical review of the manuscript
JF provided advice on lab-based testing, carried out and imaged cell-based assays
SRi provided advice on lab-based testing and critical review of the manuscript
MO provided supervision of the manuscript preparation and critical review of the manuscript.
All authors have approved the uploaded draft.

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Table 1: Comparison of paediatric nodal/paranodal seropositive patients compared to seronegative controls.

	Seropositive (n=7)	Seronegative (n=31)
Initial clinical diagnosis of GBS	4/7 (57%)	5/13 (38%)
Acute/subacute progression	3/7 (42%)	9/13 (69%)
Ataxia	3/7 (42%)	3/13 (23%)
Tremor	2/7 (28%)	2/13 (15%)
Neuropathic pain	1/7 (14%)	4/13 (30%)
Cranial nerve palsy	2/7 (28%)	5/13 (38%)
Autonomic dysfunction	1/7 (14%)	0/13 (0%)
Respiratory involvement	0/7 (0%)	5/13 (38%)
Nephrotic syndrome	0/7 (0%)	1/13 (7%)
MRI plexus/root abnormalities (where performed)	3/5 (60%)	7/10 (70%)
Nadir mRS >4	0/7 (0%)	4/13 (30%)
Nadir mRS (median, range)	4 (4-4)	4 (3-5)
CSF protein (g/L) (median, range)	1.35 (0.5-2.9)	1.2 (0.3-6.0)
Good response to IVIG (where administered)	3/6 (50%)	3/11 (27%)

CSF: cerebrospinal fluid; GBS: Guillain-Barre syndrome; IVIG: intravenous immunoglobulin; MRI: magnetic resonance imaging; mRS: modified Rankin score.
Note: 31 patients tested seronegative but phenotypic data only available for 13/31 patients

Appendix 1- Summary of cases

		Case 1	Case 2	Case 3	Case 4
Patient Demographics At Presentation	Age	5 years 8 months	5 years 3 months	2 years 8 months	2 year 3 months
	Sex	Male	Male	Male	Female
	PMHx/FHx	Nil	Nil	Nil	Nil
	Follow up (to October 2022)	2 years	7 years	21 months	3 years
Clinical Features	General	Progressive lower limb weakness over 10 days	Lower limb weakness	Profound ascending weakness over 2-4 months, poor truncal stability	Progressive lower limb weakness over 6 weeks
	Power	mRS 4; MRC: upper limbs 5/5, hip flexion 4/5, knee extension 3+/5, ankle	Hip flexion and extension 3/5; shoulder power 4/5.	Distal power 1-2/5 in the lower limbs; hip flexion 3/5. Upper limb power ranged 2-3/5.	

		dorsiflexion 2/5 and 3/5 right and left respectively			
	Reflexes	Absent in ankles bilaterally and left knee. Right knee and upper limbs: present only with reinforcement	Absent	Absent	Absent
	Ataxia	Yes	No	No	No
	Tremor	No	No	No	No
	Neuropathic pain	Yes	No	Yes	No
	Cranial nerve involvement	No	No	No	No
	Autonomic dysfunction	No	No	No	No
	Renal dysfunction	No	No	No	No
	Potential precipitating factors	Tick removed from scalp 10 days prior	Nil identified	Immunisations 5 months prior; possible viral infection 4 months prior	Nil identified
Investigations	MRI brain and spine	Smooth enhancement of the bilateral third cranial nerves, mid and lower cervical nerve roots and cauda equina nerve roots	NAD	Enhancement of cauda equine nerve roots	Initial MRI normal (non-contrast) Repeat MRI- Mild contrast enhancement of cauda equina nerve roots
	CSF protein	2.3g/L; 4.7g/L at 5 weeks	0.52g/L; 0.68g/L at 2 months	1.05g/L	1.9g/l initial 12 months later- 0.8g/l
	CSF WCC	<1 x 10^6/L	2 x 10^6/L	17 x 10^6/L	2 x 10^6/L
	CSF culture/virology	Negative	Negative	Scanty growth of cutibacterium acnes (likely contaminant)	Negative
	CSF oligoclonal bands	Negative	Paired oligoclonal bands in serum and CSF	Negative	Negative
	Nerve conduction studies (Referenced against normal paediatric values [15])	Generalised large fibre sensorimotor peripheral neuropathy with significant axonal loss particularly in the lower limb; features suspicious of peripheral nerve demyelination with reduced median/ulnar forearm conduction velocities and prolonged right tibial distal motor latency Motor NCS: Right	Initially absent F waves only; repeat after 4 years showing multifocal sensory and motor neuropathy Sensory NCS after 4 years (right sural – lateral malleolus): Velocity 36.1m/s Motor NCS after 4 years: Right median- APB: Amplitude 5.2mV, Velocity 35.7m/s (elbow – wrist); Right ulnar- ADM:	No sensory responses from right foot or right hand. Abnormal motor responses of reduced amplitude with dispersion and very slow conduction velocities and prolonged distal latencies. F-wave responses difficult to detect. Appearance of some conduction block and dispersion. Motor NCS: Left median- APB: Amplitude 0.8mV, Velocity 9m/s (elbow – wrist); Left ulnar- ADM: Amplitude 0.9mV,	The sural sensory nerve responses are unrecordable on either side, and there is attenuation of the plantar response with mild slowing of conduction. From the upper limb the median sensory nerve responses are within normal limits. Motor nerve responses from the lower limbs (tibial nerve/abductor

		peroneal: not recorded; right tibial-ankle (AHB): Amplitude 0.03mV. Right median- APB: Amplitude 4.9mV, Velocity 32m/s (elbow – wrist); Right ulnar- FDI: Amplitude 1.36mV, Velocity 38m/s (wrist – above elbow) Sensory NCS: Right radial sensory (forearm – snuff box): Amplitude 7.6μV, Velocity 55m/s; Right sural sensory (calf - ankle): Amplitude 11.9μV, Velocity 36m/s	Amplitude 7.8mV, Velocity 40m/s (wrist – above elbow); Right peroneal- EDB: Amplitude 2.5mV, Velocity 30.8m/s (popliteal fossa – fibula head)	Velocity 13m/s (wrist – above elbow); Right peroneal- EDB: Amplitude 0.5mV, Velocity 9m/s (popliteal fossa – fibula head)	hallucis) are remarkable for significant reduction of amplitude and marked prolongation of distal latencies. The left tibial nerve is inexcitable in the popliteal fossa, and F responses are very prolonged and dispersed. From the upper limb the median motor nerve responses are preserved with prolongation of distal latency and normal conduction velocity from the intermediate segment; F responses are absent. Needle electromyography shows active severe denervation with neurogenic change from the leg muscles. Overall, therefore there is evidence for a large fibre polyneuroradiculopathy with multisegmental demyelination and sensorimotor axonal loss that is prominent in the lower limbs. The findings are compatible with a subacute or chronic inflammatory process. Motor Left peroneal: not recorded; right knee-ankle: Amplitude 0.49mV. Velocity -43.5m/s

					Sensory NCS: Right and left sural sensory (calf - ankle): not recordable Right digitIII to median wrist: Amplitude 28.7mV, Velocity 58m/s
	Borrelia serology	Negative	NA	Negative	NA
	COVID-19 PCR/ known contact	Negative	NA	Negative	Negative
Antibodies	GQ1b	<25	NA	NA	Negative
	MAG	<1000 BTU	NA	NA	NA
	NF155	Positive	Positive	Negative	Positive
	NF186	Positive	Positive	Positive	Negative
	NF140	Positive	Positive	Positive	Negative
	CNTN1	Negative	Negative	Negative	NA
	CASPR1	Negative	Negative	Negative	NA
Outcome	Initial admission	8 days	3 days	4 weeks	
	Response to IVIG	3 weeks of improvement/ stabilisation (mRS 2 after 5 days) before relapse at 5 weeks. Subsequent relapses showed slower improvement	Good; continued 3 weekly infusions with normal power (5/5) throughout. Relapse of symptoms in the absence of IVIG infusions.	Excellent initial response. Relapse at 3 months and no further IVIG administered following allergic reaction	Poor, continued to deteriorate
	Other therapies	NA. Steroid therapy and rituximab declined by the family given ongoing clinical response to IVIG.	Steroids: discontinued due to behavioural issues MMF: discontinued due to side effects Rituximab: good initial response but flu-like illness with repeat infusions therefore discontinued	Methylprednisolone: good initial response although relapsed at 8 months post initial presentation. Parents declined Rituximab	Prednisolone and Dexamethasone- good response with complete resolution thus far.
	Readmissions	Yes: at 5 and 11 weeks due to relapsing symptoms	Nil	Yes: relapses at 3 months and 8 months	One after initial presentation due to worsening symptoms

ADM: abductor digiti minimi; AHB: abductor hallucis brevis; APB: abductor pollicis brevis; BTU: Buhlmann titre units; CASPR1: anti-contactin-associated protein 1 antibodies; CNTN1: anti-contactin 1 antibodies; CSF: cerebrospinal fluid; EDB: extensor digitorum brevis; FDI: first dorsal interosseous; FHx: family history; GQ1b: anti-ganglioside Q1b antibodies; IVIG: intravenous immunoglobulin; MAG: myelin associated glycoprotein antibodies; MMF: mycophenolate mofetil; MRC: Medical Research Council; MRI: magnetic resonance imaging; mRS: modified Rankin score; m/s: metres per second; mV: millivolts; NA: not applicable; NAD: no abnormality detected; NCS: nerve conduction studies; NF140: anti-neurofascin 140

antibodies; NF155: anti-neurofascin 155 antibodies; NF186: anti-neurofascin 186 antibodies; PCR: polymerase chain reaction; PMHx: past medical history; g/L: grams per litre; WCC: white cell count.