

# Antibodies to nodal/paranodal proteins in paediatric immune-mediated neuropathy

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Patients with nodal/paranodal antibodies represent a specific subgroup of inflammatory peripheral neuropathies, whose clinical presentation with a prolonged subacute phase, additional symptoms such as ataxia and tremor, and poor treatment response to IV immunoglobulin (IVIG) often differs from classic Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP).<sup>1</sup>

Previous studies on nodo/paranodopathies mainly focused on adult patients, whereas the clinical spectrum of pediatric patients is less well established. We reviewed the clinical presentation of 54 children with GBS (n = 42) and CIDP (n = 12) and retrospectively screened for antibodies against neurofascin155 (NF155), NF186, NF140, contactin-1 (CNTN1), contactin-associated protein1 (CASPR1), and glycine-receptor (GlyR) using cell-based assays<sup>2,3</sup>; 1 patient was additionally tested with CNTN1-ELISA.<sup>4</sup> All cases with sufficient serum were tested for ganglioside-IgG-, IgA-, and IgM-antibodies against GM1 (n = 42), GD1a (n = 18), GD1b (n = 23), and GQ1b (n = 21).<sup>5</sup> Clinical and paraclinical information of all patients is summarized in the table. The study was approved by the ethics committee (EK1773/2016).

## Children with classic GBS

Of 42 children with GBS, 26 were classified as acute inflammatory demyelinating polyneuropathy (AIDP), 7 as acute motor/motor-sensory axonal neuropathy (AMAN/AMSAN) by nerve conduction velocity according to Hadden criteria,<sup>6</sup> 4 as Miller-Fisher syndrome (MFS), and 2 as MFS/GBS overlap. Three patients with GBS could not be classified because of lack of nerve-conduction studies. In 25 of 35 patients (71.4%), an infection was reported within 4 weeks before symptom onset (13 gastrointestinal, 4 respiratory, and 8 unspecified). Eight patients had IgG-ganglioside antibodies (19.0%), 6 IgM (14.2%), and 1 IgA (2.4%). Nodal/paranodal antibodies were not detected. Patients with AMAN/AMSAN (5/7 with reported infection: 1 campylobacter jejuni, 1 varicella-zoster virus, and 3 unspecified) were more often ganglioside antibody positive (6/7) than patients with AIDP (4/26; likelihood ratio 12.419) or MFS (2/4).

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**Table** Clinical and paraclinical data of patients with GBS and CIDP

	GBS (42)		CIDP (12)	
	Ganglioside abs pos. (IgG/IgM/IgA)	Seronegative	Nodal/paranodal antibodies pos.	Seronegative
<b>No. of patients</b>	15	27	5	7
<b>Age mean (range)</b>	11.6 (4–17)	10.22 (1–18)	7.9 (3–11)	10.4 (4–18)
<b>Gender m:f</b>	9:6	15:12	3:2	4:3
<b>AIDP</b>	4	22		
<b>AMAN/AMSAN</b>	6	1		
<b>MFS/MFS overlap</b>	3/1	1/1		
<b>GBS no NCS</b>	1	2		
<b>GM1+</b>	6	—	0	0
<b>GD1a+</b>	1		0	0
<b>GD1b+</b>	1		0	0
<b>GM1+GD1b+</b>	4		0	0
<b>GQ1b+</b>	1		0	0
<b>GM1+GD1a+ GQ1b+</b>	1			
<b>GD1a+GQ1b+</b>	1			
<b>Pan-neurofascin+</b>	—	—	2	0
<b>NF155+</b>			1	0
<b>CNTN1+</b>			2	0
<b>CSF mean cell count/<math>\mu</math>L (range)</b>	3.15 (0–11)	2.92 (0–11)	4.6 (0–21)	3.8 (1–9)
<b>CSF mean total protein mg/dL (range)</b>	98.08 (10–250)	118.59 (19–401)	292.4 (75–619)	107.7 (24–288)
<b>Infection (data available from 45/54)</b>	11 (2 C. jejuni; 1 VZV; 8 unspecified)	14 (2 C. jejuni; 3 VZV; 1 EBV; 8 unspecified)	1	2
<b>GI</b>	6	7	1	0
<b>Respiratory</b>	2	2	0	2
<b>Other</b>	3	5	0	0
<b>Infection d prior mean (range)</b>	9 (1–14)	11.6 (3–28)	0	4.8 (1–10)
<b>Days hospitalization mean (range)</b>	13.43 (3–30)	20.73 (0–135)	13 (2–28)	10.4 (2–16)
<b>Cranial nerve involvement</b>	3	7	1	2
<b>Autonomic dysfunction</b>	1	2	0	0
<b>Tremor/ataxia</b>	3	3	5	1
<b>Outcome mRS (available from 32/42 GBS and 11/12 CIDP)</b>	11 mRS 0–1; 1 mRS 2–4; 1 mRS >1;	15 mRS 0–1; 4 mRS 2–4; 1 mRS 5–6; 5 mRS >1;	2 mRS 0–1; 3 mRS 2–4; 3 mRS >1;	2 mRS 0–1; 4 mRS 2–4; 4 mRS >1;
<b>Severity at nadir HS (available from 41/42 GBS and 12/12 CIDP)</b>	2 HS1; 8 HS2; 1 HS3; 2 HS4; 1 HS5	2 HS1; 5 HS2; 7 HS3; 6 HS4; 6 HS5; 1 HS6	3 HS3; 2 HS4	2 HS1; 1 HS2; 4 HS4

Abbreviations: AIDP = acute inflammatory demyelinating polyneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor and sensory axonal neuropathy; C. jejuni = campylobacter jejuni; CIDP = chronic inflammatory demyelinating polyneuropathy; EBV = Epstein-Barr virus; GBS = Guillain-Barré syndrome; GI = gastrointestinal; HS = Hughes score; MFS = Miller-Fisher syndrome; mRS = modified Rankin Scale; NCS = nerve-conduction study; VZV = varicella-zoster-virus.

## Children with nodal/paranodal antibodies

Five of 12 children, who met the EFNS/PNS criteria for CIPD, had nodal/paranodal antibodies: 2 pan-neurofascin (NF155/NF186/140 triple positive), 1 NF155, and 2 CNTN1-antibodies. The IgG-subclass distribution was determined by flow cytometry analysis.<sup>7</sup> IgG4 was the predominant subclass in all patients and ranged from 75% to 100%. In addition, 1 patient with pan-neurofascin-antibodies tested positive for GlyR-antibodies but did not develop stiff-person syndrome or progressive encephalomyelitis with rigidity, and the significance of this finding needs further investigation. The mean age was 7.9 years (range 3–11), and the male:female ratio was 3:2. The median duration of hospitalization was 13 days (range 2–28). One pan-neurofascin-patient was initially diagnosed as GBS and reclassified as CIPD during disease course, the other patients had a chronic onset with slow progression over months or years. One child had a gastrointestinal infection before symptom onset. One CNTN1-patient showed cranial nerve involvement and optic neuritis during disease course. All children had ataxia, 4 neuropathic pain (all except 1 pan-neurofascin), and 3 (2 CNTN1, and 1 pan-neurofascin) tremor. At the peak of disease, 3 children needed a walking aid (Hughes 3) and 2 were bedridden (Hughes 4). None of the children had renal dysfunction. The mean CSF white cell count was 4.6  $\mu$ L (range 0–21), and the mean CSF protein was 292.4 mg/dL (range 75–619).

The mean time of follow-up was 32 months (range 17–57). The 2 CIPD patients with pan-neurofascin-antibodies initially showed no or only partial response to IVIG and therefore received corticosteroids, 1 along with plasma exchange and the other with mycophenolate. Both recovered only very slowly over up to 4 years with a modified Rankin Scale (mRS) score of 1 at the last follow-up. The NF155-patient did not respond to IVIG and corticosteroids and subsequently received immunoadsorption and rituximab, leading to significant clinical improvement. After 8 months, he relapsed in association with normalization of the CD19/20 ratio and again rapidly improved after another dose of rituximab, with a mRS score of 2 at the last follow-up. One patient with CNTN1-antibodies worsened despite monthly IVIG and corticosteroids given over 4 months. After treatment was switched to rituximab, he improved rapidly in the following weeks and remained stable since then. The second child with CNTN1-antibodies showed only partial response to IVIG with relapses in conjunction with infections. This child improved significantly after rituximab application with a mRS score of 2 at the last follow-up.

In summary, our study demonstrates that nodal/paranodal antibodies occur in a subgroup of paediatric patients with CIPD, but not GBS. Children with AMAN/AMSAN frequently have ganglioside antibodies. Children with CIPD and atypical/prolonged disease course with high Hughes score (>2), sensory ataxia, prominent neuropathic pain, and tremor may have nodal/paranodal antibodies. These patients often

do not sufficiently respond to IVIG, whereas in our case series, rituximab led to prompt improvement in 3 children. Optimal treatment strategies for children with nodal/paranodal antibodies have to be further determined in larger studies.

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### Disclosure

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Continued

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