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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).[1]

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[2,3]; 1 patient was additionally tested with CNTN1-ELISA.[4] 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).[5] 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,[6] 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
No. of patients	15	27	5	7
Age mean (range)	11.6 (4–17)	10.22 (1–18)	7.9 (3–11)	10.4 (4–18)
Gender m:f	9:6	15:12	3:2	4:3
AIDP	4	22		
AMAN/AMSAN	6	1		
MFS/MFS overlap	3/1	1/1		
GBS no NCS	1	2		
GM1+	6	—	0	0
GD1a+	1		0	0
GD1b+	1		0	0
GM1+GD1b+	4		0	0
GQ1b+	1		0	0
GM1+GD1a+ GQ1b+	1			
GD1a+GQ1b+	1			
Pan-neurofascin+	—	—	2	0
NF155+			1	0
CNTN1+			2	0
CSF mean cell count/μL (range)	3.15 (0–11)	2.92 (0–11)	4.6 (0–21)	3.8 (1–9)
CSF mean total protein mg/dL (range)	98.08 (10–250)	118.59 (19–401)	292.4 (75–619)	107.7 (24–288)
Infection (data available from 45/54)	11 (2 C. jejuni; 1 VZV; 8 unspecified)	14 (2 C. jejuni; 3 VZV; 1 EBV; 8 unspecified)	1	2
GI	6	7	1	0
Respiratory	2	2	0	2
Other	3	5	0	0
Infection d prior mean (range)	9 (1–14)	11.6 (3–28)	0	4.8 (1–10)
Days hospitalization mean (range)	13.43 (3–30)	20.73 (0–135)	13 (2–28)	10.4 (2–16)
Cranial nerve involvement	3	7	1	2
Autonomic dysfunction	1	2	0	0
Tremor/ataxia	3	3	5	1
Outcome mRS (available from 32/42 GBS and 11/12 CIDP)	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;
Severity at nadir HS (available from 41/42 GBS and 12/12 CIDP)	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 CIDP, 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.[7] 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 CIDP 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 μL (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 CIDP 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 CIDP, but not GBS. Children with AMAN/AMSAN frequently have ganglioside antibodies. Children with CIDP 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

D. De Simoni, G. Ricken, M. Winklehner, I. Koneczny, M. Karenfort, U. Hustedt, U. Seidel, O. Abdel-Mannan, P. Munot, S. Rinaldi, C. Steen, M. Freilinger, M. Breu, R. Seidl, M. Reindl, J. Wanschitz, C. Lleixá, G. Bernert, K.P. Wandinger, R. Junker, L. Querol, F. Leypoldt, K. Rostásy, and R. Höftberger report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

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Desiree De Simoni, MD	Medical University of Vienna, Austria; University Hospital St. Poelten, Austria	Acquisition of data, statistical analysis, execution, and interpretation of data
Gerda Ricken, MSc	Medical University of Vienna, Austria	Acquisition of data, execution, interpretation of data, and critical review for important intellectual content
Michael Winklehner, MD	Medical University of Vienna, Austria	Statistical analysis and critical review for important intellectual content
Inga Koneczny, PhD	Medical University of Vienna, Austria	Acquisition of data, execution, interpretation of data, and critical review for important intellectual content

Continued

Appendix *(continued)*

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