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Anti-AGO1 Antibodies Identify a Subset of Autoimmune Sensory Neuronopathy

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Abstract

Background and Objectives

Autoantibodies (Abs) improve diagnosis and treatment decisions of idiopathic neurologic disorders. Recently, we identified Abs against Argonaute (AGO) proteins as potential autoimmunity biomarkers in neurologic disorders. In this study, we aim to reveal (1) the frequency of AGO1 Abs in sensory neuronopathy (SNN), (2) titers and IgG subclasses, and (3) their clinical pattern including response to treatment.

Methods

This retrospective multicentric case/control study screened 132 patients with SNN, 301 with non-SNN neuropathies, 274 with autoimmune diseases (AIDs), and 116 healthy controls (HCs) for AGO1 Abs through ELISA. Seropositive cases were also tested for IgG subclasses, titers, and conformation specificity.

Results

AGO1 Abs occurred in 44 patients, comprising significantly more of those with SNN (17/132 [12.9%]) than those with non-SNN neuropathies (11/301 [3.7%]; $p = 0.001$), those with AIDs (16/274 [5.8%]; $p = 0.02$), or HCs (0/116; $p < 0.0001$). Ab titers ranged from 1:100 to 1:100,000. IgG subclass was mainly IgG1, and 11/17 AGO1 Ab-positive SNN (65%) had a conformational epitope. AGO1 Ab-positive SNN was more severe than AGO1 Ab-negative SNN (e.g., SNN score: 12.2 vs 11.0, $p = 0.004$), and they more frequently and more efficiently responded to immunomodulatory treatments than AGO1 Ab-negative SNN (7/13 [54%] vs 6/37 [16%], $p = 0.02$). Regarding the type of treatments more precisely, this significant difference was confirmed for the use of IV immunoglobulins (IVIg) but not for steroids or second-line treatments. Multivariate logistic regression adjusted for potential confounders showed that AGO1 Ab positivity was the only predictor of response to treatment (OR 4.93, 1.10–22.24 95% CI, $p = 0.03$).

Discussion

Although AGO Abs are not specific for SNN, based on our retrospective data, they may identify a subset of cases with SNN with more severe features and a possibly better response to IVIg. The significance of AGO1 Abs in clinical practice needs to be explored on a larger series.

*These authors contributed equally to this work.

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Glossary

Abs = autoantibodies; **AD-AID** = associated definite autoimmune disease; **AGO** = Argonaute; **CBA** = cell-based assay; **DRG** = dorsal root ganglia; **DSS** = deep and superficial sensation; **ENMG** = electroneuromyography; **HCs** = healthy controls; **IVIg** = intravenous immunoglobulins; **mRS** = modified Rankin score; **ND-AID** = nondefinite autoimmune disease; **ONP** = other neuropathies; **SFN** = small fiber neuropathy; **SjS** = Sjögren syndrome; **SNN** = sensory neuronopathy.

The identification of specific autoantibodies (Abs) in neurologic disorders of unknown origin greatly improves their diagnostic and treatment decisions.¹⁻⁴ In several conditions, Abs suffice to define an entire entity. This is the case for anti-N-methyl-D-aspartate receptor Abs, which define a subtype of autoimmune encephalitis, where the Abs are probably also responsible for symptoms, and patients improve with immunomodulatory treatments.⁵ Other antibodies that are probably not the primary cause of the disease nevertheless serve as diagnostic biomarkers. For example, onconeural antibodies ascribe a neurologic disorder to a paraneoplastic origin and help the search for the underlying tumor.⁶ Recently, we have shown that Abs targeting Argonaute (AGO) proteins, a family of 4 RNA-binding proteins, are rather nonparaneoplastic biomarkers of an autoimmune context in disorders of the peripheral and CNS.⁷ These Abs mostly reacted with AGO1 and 2, and sensory neuronopathy (SNN) was the most frequent manifestation.⁷ Two-thirds of the patients had an accompanying autoimmune comorbidity—mainly Sjögren syndrome (SjS)—in keeping with previous studies that detected AGO Abs in 3%–32% of patients with systemic autoimmune diseases (AIDs).⁸⁻¹⁰

SNN is a usually disabling disorder resulting from the degeneration of sensory neurons in dorsal root ganglia (DRG) and depends on multiple mechanisms including paraneoplastic, toxic, viral, and genetic ones.¹¹ Other cases occur with systemic autoimmune diseases, especially SjS, while some remain of undetermined origin. Among the latter are inflammatory SNN that can theoretically be diagnosed by DRG biopsy only. Therefore, there is a need for a less invasive identification of these and other cases with an overt autoimmune context that may respond to immunomodulatory treatments. Only 8 patients with SNN with anti-AGO1 Abs were described in our first study, not allowing for valid statements on the potential diagnostic or therapeutic benefits of AGO Ab detection in SNN.⁷

In this study, we aim to reveal the (1) frequency of AGO1 Abs in SNN, (2) titers and IgG subclasses, and (3) clinical pattern and treatment response of AGO Ab-associated SNN. We provide evidence that anti-AGO1 Abs are overrepresented in SNN and occur in patients with and without associated autoimmune context and that AGO1 Ab-associated SNN represent a subset with more severe features and a potentially better response to IVIg treatment.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the ethical committee of the University Hospital of Saint-Etienne, France (IRBN742021/CHUSTE) and conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants provided written informed consent. The privacy rights of human subjects were observed. No animal experiments were conducted.

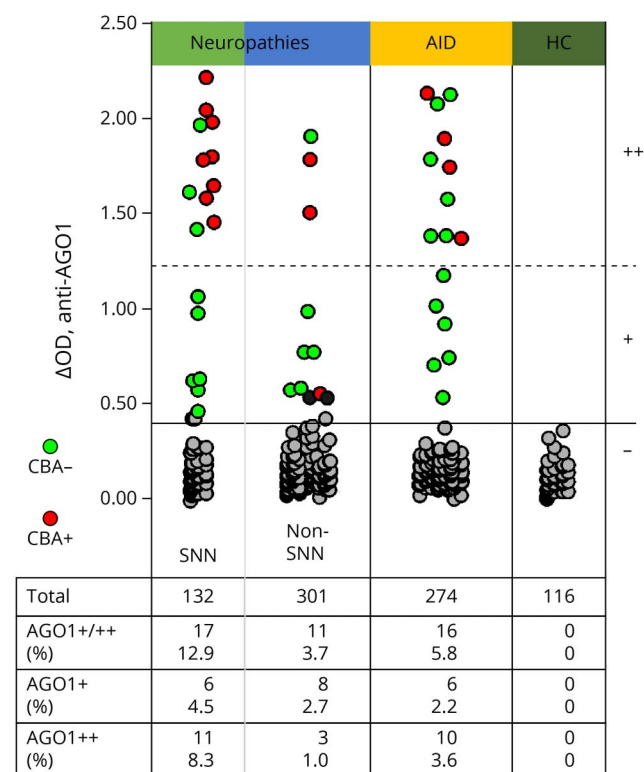
Study Design, Patients, and Controls

In a retrospective multicentric case/control and observational study conducted in expert neuromuscular centers, we tested 132 patients with SNN,¹² 301 patients with non-SNN peripheral neuropathy. Patients were distinguished regarding the presence or absence of an associated autoimmune context. “With autoimmune context” indicated an associated definite autoimmune disease (AD-AID) or the presence of nonorgan-specific Abs without fulfillment of the criteria of an AID (ND-AID; eFigure 1; details in eMethods, links.lww.com/NXI/A817). Controls consisted of 274 patients with AID and no peripheral neuropathies and 116 healthy controls (HCs; details in eMethods, links.lww.com/NXI/A817). Study size was reached by using all available sera. In total, the sera of 192 individuals of this study have been included in our first clinical description,⁷ comprising 124 patients with AID, 22 with SNN, 1 with small fiber neuropathy (SFN), and 33 with other neuropathies (ONP). Ten of those previously reported patients were anti-AGO1–positive, comprising 7 cases with SNN, 1 with SFN, and 2 with ONP.

Collected Clinical Data

Clinical and paraclinical data were obtained by sending to the referring physicians a form collecting information on the final diagnosis of the neuropathy, symptoms and signs, topography of reported symptoms as paresthesia and sensory loss, SNN score, electroneuromyography (ENMG), biological workup, associated diseases, treatment, and modified Rankin score (mRS) before and after treatment. Details regarding the calculation and the range of the SNN score are summarized in eTable 3, links.lww.com/NXI/A817. We decided to use the mRS scale because our study was retrospective. Two evaluations were requested. The first described the patient status when signs and symptoms of the neuropathy were fully developed to allow its diagnosis (full development of the neuropathy), and the second retrospectively collected data

Figure 1 Screening of 823 Individuals for AGO1 Abs Through ELISA and Resulting Frequency in Different Study Groups



Serum reactivities (shown as Δ ODs) with AGO1 of 823 individuals among 4 study groups through ELISA. The solid line at Δ OD = 0.386 represents the $z = 4$ cutoff line to define seropositivity. The dashed line at Δ OD = 1.21 ($z = 14$) distinguishes between moderately positive (+) and strongly positive (++) individuals. Results of CBA testing are represented by green (CBA negative) and red (CBA positive) points. Absolute and relative numbers of seropositive cases are listed in the table below the graph. Abs = autoantibodies; AGO = Argonaute; CBA = cell-based assay; Δ OD = difference between optical densities of coated and uncoated wells.

concerning the neuropathy onset (see details in eMethods, links.lww.com/NXI/A817). A third evaluation obtained at least 6 months later was left to the discretion of the investigators. All the referring physicians were blind to the anti-AGO Ab results.

Response to Immunomodulatory Treatments

Immunomodulatory treatments were classified into 2 groups: first-line treatments included steroids, IV immunoglobulins (IVIg), and plasma exchanges; second-line treatments included azathioprine, cyclophosphamide, mycophenolate mofetil, and rituximab. The response to treatment was evaluated by analyzing the evolution of the mRS before and after treatment: (1) a reduction of at least 1 point on the mRS classified the patient as “responder” to treatment or classified the patient in the “improvement” group; (2) an increase of at least 1 point on the mRS after treatment classified the patient in the “disease progression” group; (3) an equality of the mRS between before and after treatment classified the patient in the “stabilization” group. The percentage of responders was then measured in patients with SNN with or without AGO1 Abs. We also calculated (1) the median values of the mRS before and after treatment and the

median of the corresponding mRS differences in patients with SNN with or without AGO1 Abs and (2) the median values of the mRS at the first and the last clinical evaluation and the corresponding median of the mRS differences in patients with SNN without AGO1 Abs and without immunomodulatory treatment.

Serum Collection

Sera from patients were obtained from our biobank (CRB42 CHU Saint-Etienne, France, AC 2018–3372, NFS96-900, N° of collection DC-2010-1108). HC sera were obtained from the blood donation service of the French Blood Establishment. Samples were collected from October 1998 to January 2021, prepared, and stored, as previously described.¹³

Detection of Serum Anti-AGO1 and AGO2 Abs Through ELISA and Cell-based Assay

Because our recent discoveries have revealed AGO1 as the most sensitive antigen,^{7,14} we used our AGO1 ELISA data for this study.¹⁴ ELISA reactivity with AGO2 was then tested for all AGO1 Ab-positive sera. Abs were detected through our previously reported protocol^{14,16} with some modifications. “AGO1/2 Ab-positive” (+ or ++) has been defined as a reactivity of ≥ 4 SD above the mean reactivity of 116 (for AGO1 Abs) or 13 (for AGO2 Abs) HCs. “Moderately positive” (+) and “strongly AGO Ab-positive” (++) have been defined as a reactivity of 4–14 SD and ≥ 14 SD, respectively, above these mean reactivities of HCs. The reason for distinguishing these 2 levels of positivity was the probable presence of 2 levels of ELISA reactivities. This was confirmed by significantly differing cell-based assay (CBA) positivity rates between the 2 levels.¹⁴ All patients who were tested positive in ELISA were tested in CBA using the same protocol as in our previous study.⁷ The antibody titer was determined by serial dilutions of the sera in ELISA at 1:100, 1:1,000, 1:10,000, 1:100,000, and 1:1,000,000. More details about the ELISA analyses can be found in our parallel methodological article.¹⁴

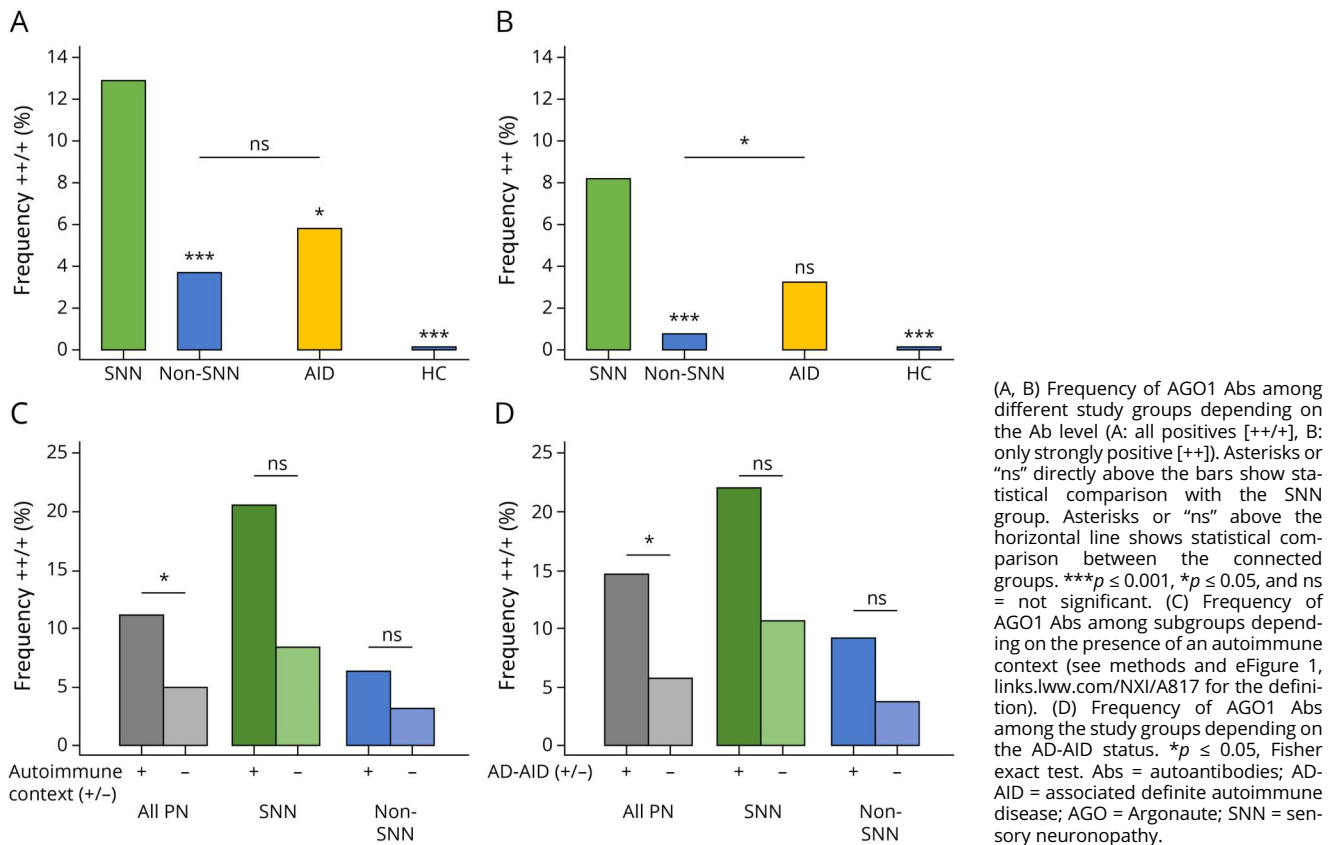
Detection of Conformation-Specific AGO1 Abs Through Comparative Denaturing/Stabilizing ELISA

We applied the comparative denaturing/stabilizing ELISA¹⁴ for all the AGO1 Ab-positive patients. In brief, this assay was an ELISA with 3 conditions of AGO1 protein: standard conditions (using a common coating buffer without glycerol), stabilizing conditions (30% glycerol in coating buffer), and linearizing conditions (i.e., denaturing conditions using 0.8% sodium dodecyl sulfate). All remaining steps were performed as mentioned earlier for the common ELISA. Patients with conformational AGO1 Ab epitopes were defined as those among AGO1 Ab-positive patients losing $\geq 50\%$ of their ELISA reactivity under denaturing conditions when compared with that under stabilizing conditions. Patients with linear epitopes were defined as those losing $< 50\%$ under denaturing.¹⁴

Statistical Analysis

Clinical and paraclinical data were compared among groups as previously published.¹⁵ More details are available in the eMethods, links.lww.com/NXI/A817.

Figure 2 AGO Ab Frequency in Different Disease Groups and Subgroups With and Without Autoimmune Context



Data Availability

All anonymized data from this study or all related documents will be shared by request from any qualified investigator.

Results

Frequency and Distribution of AGO1 Abs

Among the 823 individuals tested through ELISA, 44 had AGO1 Abs (Figure 1). None of the 116 HCs showed positive results. Of the 132 patients with SNN, 17 (12.9%) were AGO1 Ab positive. Of the 301 patients with non-SNN neuropathy, 11 (3.7%) showed positive results (Figure 1), including 4 (3.6%) of 116 patients with chronic inflammatory demyelinating polyneuropathy, 3 (3.8%) of 80 patients with SFN, and 4 (4.0%) of 105 patients with ONP. Of the 274 patients with AIDs, 16 (5.8%) were AGO1 Ab positive (Figure 1).

The frequency of AGO1 Ab–positive individuals was significantly higher in the SNN cohort compared with patients with non-SNN neuropathies ($p = 0.001$, Fisher exact test), patients with AIDs ($p = 0.02$), and HCs ($p < 0.0001$; Figure 2A). When taking only strongly AGO1 Ab–positive cases into account, a similar frequency distribution was observed, but no significant differences were found when comparing with the

AID group (Figure 2B). In patients with a peripheral nervous system disorder as a whole, AGO1 Ab positivity was more frequent in patients with than those without an autoimmune context (19/169 [11.2%] vs 9/187 [4.8%], $p = 0.03$; Figure 2C). More specifically, AGO1 Ab positivity was more frequent in patients with than those without AD-AID (12/80 [15.0%] vs 16/281, 5.7%, $p = 0.02$; Figure 2D). This did not reach significance when considering the SNN or non-SNN subgroups separately, probably due to the smaller sample size. Among SNN, AGO1 Abs were detected in 5/59 (8.5%) patients without other clinical or biological autoimmune context (Figure 2C).

Because several patients who tested positive for AGO1 Abs received IVIg and to verify whether prior IVIg might have had an impact on the AGO status, we tested 2 AGO Ab–negative patients with a sampling before and immediately after IVIg treatment. Their status remained negative on treatment (data not shown).

Antibody Titers, AGO2 Binding, Conformation Specificity, and IgG Subclasses

The ELISA AGO1 Ab titers ranged from 1:100 to 1:100,000 in patients with neuropathy and from 1:100 to 1:10,000 in the AID cohort. Among the 17 AGO1 Ab–positive patients with SNN tested for antibody titers by ELISA, 8 (47.1%) had

Table 1 Clinical Characterization of AGO1 Ab-Positive Patients With SNN in Comparison With AGO1 Ab-Negative Patients With SNN

Parameters	AGO1-positive patients with SNN	AGO1-negative patients with SNN	p Value
Clinical characteristics at the onset of neuropathy			
Age, median y (25th–75th percentile)	50 (42.5–54.2)	49.5 (37.1–61)	0.71
Sex, F/M (% of F)	12/5 (71%)	62/43 (59%)	0.37
Course, N (%)			
Acute	3/17 (18%)	8/79 (10%)	0.38
Subacute	4/17 (24%)	18/79 (23%)	0.95
Progressive	10/17 (59%)	53/79 (67%)	0.52
Symptoms reported by patient, N (%)			
Paresthesia/dysesthesia	16/17 (94%)	60/76 (79%)	0.15
Pain	10/17 (59%)	36/76 (47%)	0.40
Ataxia	10/15 (67%)	46/76 (61%)	0.66
Topography of reported symptoms, N (%)			
Purely LL	3/17 (18%)	27/77 (35%)	0.17
Including UL	11/17 (65%)	42/77 (55%)	0.45
Asymmetry	9/17 (53%)	32/73 (44%)	0.50
Clinical characteristics at full development of the neuropathy			
Delay, median y (25th–75th percentile)	2 (0.3–9.8)	3.1 (1–6)	0.65
SNN score, median (25th–75th percentile)	12.2 (11–12.7)	11 (8.2–11)	0.004
Symptoms reported by patient, N (%)			
Paresthesia	15/17 (88%)	59/76 (78%)	0.33
Dysesthesia	12/17 (71%)	39/76 (51%)	0.15
Pain	9/17 (53%)	38/76 (50%)	0.83
Topography of reported symptoms, N (%)			
Purely LL	0/17 (0%)	12/76 (16%)	0.08
Including UL	17/17 (100%)	63/76 (83%)	0.07
Asymmetry	8/17 (47%)	34/76 (45%)	0.86
Clinical signs at clinical examination, N (%)			
Purely PTS altered (unmyelinated sensory fibers)	1/15 (7%)	3/74 (4%)	0.40
Purely DSS altered (myelinated sensory fibers)	3/15 (20%)	18/74 (24%)	0.56
PTS + DSS altered	14/17 (82%)	53/74 (72%)	0.32
Face included	8/17 (47%)	14/75 (19%)	0.01
Trunk included	5/16 (31%)	15/75 (20%)	0.33
Ataxia UL	13/16 (81%)	43/74 (58%)	0.09
Ataxia LL	14/16 (88%)	53/74 (72%)	0.19
Global areflexia	13/17 (76%)	29/75 (39%)	0.01
Dysautonomia	5/16 (31%)	17/76 (22%)	0.45

Continued

Table 1 Clinical Characterization of AGO1 Ab–Positive Patients With SNN in Comparison With AGO1 Ab–Negative Patients With SNN (continued)

Parameters	AGO1-positive patients with SNN	AGO1-negative patients with SNN	<i>p</i> Value
AD-AID, N (%)	8/17 (47%)	28/101 (28%)	0.11
SjS	6/8 (75%)	12/28 (43%)	0.01
SLE	0/8 (0%)	3/28 (11%)	0.47
Other	2/8 (25%)	13/28 (46%)	0.90
ND-AID, N (%)	4/17 (24%)	31/101 (31%)	0.55
Other autoantibodies, N (%)^a	11/17 (65%)	51/101 (51%)	0.31
No. of patients without autoimmune diseases or autoantibodies (%)	5/17 (29%)	—	
Other associated diseases, N (%)			
Cancer	2/17 (12%)	7/101 (7%)	0.49
Diabetes	0/17 (0%)	7/101 (7%)	0.27

Abbreviations: AD-AID = associated definite autoimmune diseases; DSS = deep and superficial sensation; F = female; LL = lower limbs; LLN = lower limit of the normal; M = male; N = number; ND-AIDs = nondefinite autoimmune diseases; PTS = pain and temperature sensation; SjS = Sjögren syndrome; SLE = systemic lupus erythematosus. ^a Autoantibodies in AGO1-positive patients: antinuclear antibodies (11/11 with 5/11 SSA, 3/11 SSB), anti-FGFR3 (4/11), antismooth muscles (1/11), rheumatoid factors (1/11); autoantibodies in AGO1-negative patients: antinuclear antibodies (27/51 with 8/51 SSA, 6/51 SSB), anti-FGFR3 (38/51), anti-H+/K + ATPase or anti-intrinsic factor or antiparietal cells (3/51), anti-gangliosides (6/51), rheumatoid factors (6/51), antismooth muscles (1/51), and antineutrophil cytoplasmic antibodies (1/51). Bolded *p* values are statistically significant (*p* < 0.05).

AGO1 Ab titers $\geq 1:10,000$ (eFigure 2, links.lww.com/NXI/A817). Of note, of the 5 patients with titers $\geq 1:100,000$ among all study groups, 4 had SNN.

Among 16 AGO1 Ab–positive patients with SNN tested for the presence of AGO2 Abs, 10 (62.5%) showed positive results (eFigure 2, links.lww.com/NXI/A817). Among the 17 AGO1 Ab–positive patients with SNN tested for conformation specificity, 11 (64.7%) bound a conformation-specific epitope (eFigure 2, links.lww.com/NXI/A817).

There were no significant differences between the disease groups regarding the proportion of individuals with high-titer antibodies, presence of AGO2 Abs, or conformation-specific reactivity (*p* = 0.67, *p* = 0.25, and *p* = 0.48, respectively, χ^2 over all groups).

Regarding the IgG subclass, the most common subclass among the AGO1 Ab–positive patients with SNN was IgG1 (15/17, 88.2%), followed by less common subclasses IgG4 (4/17, 23.5%), IgG3 (3/17, 17.6%), and IgG2 (1/17, 5.9%; eFigure 2, links.lww.com/NXI/A817). There were no significant differences regarding IgG subclass among the tested study groups (IgG1 *p* = 0.95; IgG4 *p* = 0.80; IgG3 *p* = 0.81; and IgG2 *p* = 0.90, χ^2 over all groups).

Clinical Characteristics of AGO1 Ab–Positive SNN

To determine whether AGO1 Ab–positive SNN had distinctive features, we compared the 17 AGO1 Ab–positive patients with SNN (eTable 1, links.lww.com/NXI/A817, summarizes their individual clinical and paraclinical data) with the 115 AGO1 Ab–negative patients with SNN regarding

demographical, clinical, and paraclinical data (Table 1) and ENMG data (Table 2). A statistical bootstrapping analysis that was applied to control for the unequal sample sizes confirmed all significant differences reported further.

There were no differences concerning age, sex, the initial presentation of the neuropathy, and the disease course. At full development of the disease, the SNN score was significantly higher in AGO1 Ab–positive than in AGO1 Ab–negative patients with SNN (Table 1). Paresthesia and dysesthesia in the face and global areflexia were more frequent. Concerning the presence of AD-AID, SjS was more frequent for AGO1 Ab–positive than negative patients with SNN. Regarding ENMG, the number of abolished sensory nerve action potentials was higher in AGO1 Ab–positive than in negative patients with SNN (Table 2).

Multivariate logistic regression adjusted for age and sex found that AGO1 Ab–positive patients with SNN had a significantly higher mRS before treatment (OR 3.63, 1.74–7.57 95% CI, *p* = 0.001), more frequent global areflexia (OR 5.06, 1.00–25.6 95% CI, *p* = 0.05), and more frequent SjS (OR 6.63, 1.26–34.96 95% CI, *p* = 0.03) than seronegative patients with SNN. The area under the curve of the logistic regression model was 0.90 (95% CI: 0.81–0.95, *p* < 0.0001) suggesting that clinical features of AGO1 Ab–positive patients with SNN differ from those of the seronegative patients with SNN.

Response to Treatment in Patients With SNN With Anti-AGO1 Abs

Information on treatment was available for 93/132 (70.5%) patients with SNN (AGO1 Ab positive: 16/17 [94.1%];

Table 2 Electrophysiologic Characterization of AGO1 Ab–Positive Patients With SNN in Comparison With AGO1 Ab–Negative Patients With SNN

Parameters	AGO1-positive patients with SNN	AGO1-negative patients with SNN	<i>p</i> Value
Delay, mean $y \pm$ SEM	7.1 \pm 2.3	6.4 \pm 0.8	0.58
Sensory nerve conduction, mean N \pm SEM (mean %)			
UL			
No. of tested nerves	5.4 \pm 0.3	4.8 \pm 0.2	0.17
N abnormal SNAPs	4.9 \pm 0.3 (91.7%)	4.2 \pm 0.2 (86.6%)	0.19
N abolished SNAPs	2.6 \pm 0.5 (50%)	1.8 \pm 0.2 (38.8%)	0.11
LL			
N tested nerves	3.5 \pm 0.3	3.1 \pm 0.1	0.17
N abnormal SNAPs	3.2 \pm 0.3 (88.2%)	2.6 \pm 0.2 (83.2%)	0.06
N abolished SNAPs	2.6 \pm 0.4 (72.1%)	1.8 \pm 0.2 (55.9%)	0.046
Motor nerve conduction (all limbs), mean N \pm SEM (mean %)			
N tested nerves	5.3 \pm 0.6	6.2 \pm 0.2	0.20
N nerves with normal pattern	4.6 \pm 0.6 (79.7%)	4.8 \pm 0.2 (77.4%)	0.59
N nerves with axonal pattern	0.5 \pm 0.2 (10%)	0.6 \pm 0.1 (8.9%)	0.85
N nerves with primary demyelinating pattern	0.1 \pm 0.1 (1.9%)	0 \pm 0 (0.7%)	0.08
N nerves with mixed axonal and demyelinating pattern	0.4 \pm 0.2 (8.4%)	0.8 \pm 0.1 (13.1%)	0.20

Abbreviations: LL = lower limbs; SNAP = sensory nerve action potential; UL = upper limbs. Bolded *p* values are statistically significant ($p < 0.05$).

AGO1 Ab negative: 77/115 [67.0%]; $p = 0.02$). Among them, 57 patients received an immunomodulatory treatment (AGO1 Ab–positive: 15/16 [94%]; AGO1 Ab negative: 42/77 [55%], $p = 0.004$, eTable 2, links.lww.com/NXI/A817). The others were not treated. Among the 57 patients who received immunomodulatory treatment, 50 (87.7%) were with sufficient data to evaluate the mRS before and after treatment (AGO1 Ab positive 13/15 [86.7%]; AGO1 Ab negative: 37/42 [88.1%]; $p = 1.000$). Among the 15 anti-AGO1–positive patients who received an immunomodulatory treatment, 8 had an associated autoimmune disease, 3 had only Abs without AID, i.e., ND-AID, and 4 had no known autoimmune context.

Regarding the effect of treatment, the percentage of responders to any immunomodulatory treatment was higher in anti-AGO1–positive than negative patients with SNN (Table 3). Response to treatment was significantly associated with the presence of AGO1 Abs only for the use of first-line treatments alone. Regarding the type of treatments more precisely, response to treatment was significantly associated with the presence of AGO1 Abs for the use of IVIg but not with steroids or second-line treatments.

Multivariate logistic regression adjusted for age, sex, the SNN score, the neuropathy course (acute or not), the presence of anti-AGO Abs, and the presence of an AD-AID found that

response to treatment was associated with anti-AGO1 Abs only (OR 4.93, 1.10–22.24 95% CI, $p = 0.03$) but not with the potential confounders. In eFigure 3, links.lww.com/NXI/A817, we evaluated the overall evolution of the mRS to quantify the effect of immunomodulatory treatments (cf. supplemental data).

Potential Benefit of AGO1 Abs in Treatment Decisions

Among our patients with SNN, there were 50 with data for immunomodulatory treatment response. Among them, 13 (26%) were responders. While information of the presence of an underlying autoimmune context did not significantly distinguish responders from nonresponders, adding the information of the presence of AGO1 Abs to the decision tree resulted in significantly different frequencies of responders to treatment (Figure 3).

Discussion

This study revealed (1) a frequency of 13% for AGO1 Abs in SNN, (2) titers ranging from 1:100 to 1:100,000 of mainly IgG1 subclass, and (3) more severe features and a probably better response to IVIg treatment for AGO Ab-associated SNN.

In our previous study that included central and peripheral nervous system disorders, SNN was the most frequent one to

Table 3 Effects of Immunomodulatory Treatments in Patients With SNN

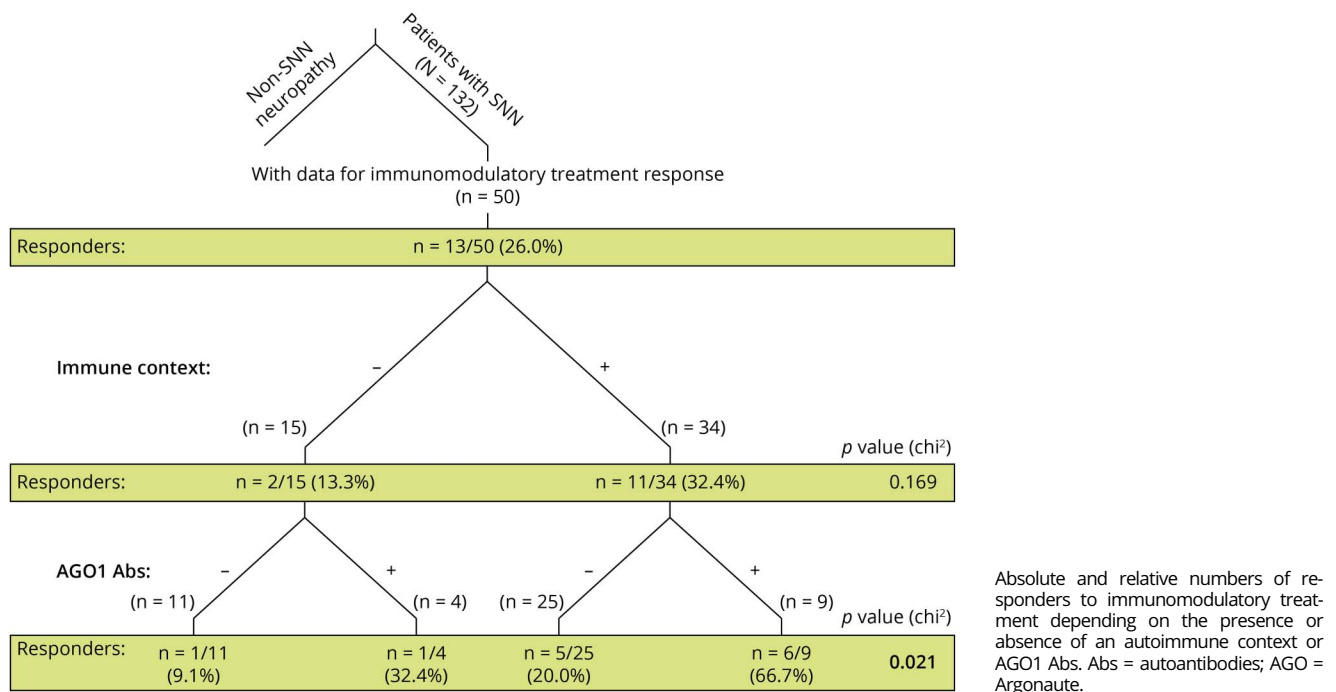
Parameters	AGO1-positive patients with SNN	AGO1-negative patients with SNN	<i>p</i> Value
mRS in patients receiving immunomodulatory treatment			
mRS before treatment			
Data available	15/15 (100%)	38/42 (90%)	0.22
Median (IQR)	4 (3–4)	2 (2–3)	0.004
mRS after treatment			
Data available	13/15 (87%)	37/42 (88%)	0.89
Median (IQR)	3 (2–4)	2 (2–3)	0.24
Decrease of mRS \geq1, N (%)	7/13 (54%)	6/37 (16%)	0.02
First-line treatment alone (IVIg, CC, and plasma exchange)	3/3 (100%)	4/18 (22%)	0.01
Second-line treatment alone	1/1 (100%)	0/3 (0%)	0.08
First-line + second-line treatment	3/9 (33%)	2/16 (13%)	0.22
IVIg	6/11 (55%)	4/22 (18%)	0.03
IVIg only	1/1 (100%)	1/7 (14%)	0.08
IVIg with only other first-line treatment	2/2 (100%)	1/6 (17%)	0.049
IVIg with only other second-line treatment	1/2 (50%)	0/2 (0%)	0.32
IVIg with other first-line and other second-line treatment	2/6 (33%)	2/7 (29%)	0.86
Steroids	3/8 (38%)	5/25 (20%)	0.32
Steroids only	0/0 (0%)	2/5 (40%)	0.65
Steroids with only other first-line treatment	1/1 (100%)	1/6 (17%)	0.11
Steroids with only other second-line treatment	0/1 (0%)	0/7 (0%)	1.00
Steroids with other first-line and other second-line treatment	2/6 (33%)	2/7 (29%)	0.86
PLEX	2/2 (100%)	1/1 (100%)	0.56
PLEX only	0/0 (0%)	0/0 (0%)	—
PLEX with only other first-line treatment	2/2 (100%)	0/0 (0%)	—
PLEX with only other second-line treatment	0/0 (0%)	0/0 (0%)	—
PLEX with other first-line and other second-line treatment	0/0 (0%)	1/1 (100%)	—
Other treatments (second-line treatment)	4/10 (40%)	2/19 (11%)	0.07
One second-line treatment only	1/1 (100%)	0/2 (0%)	0.16
One second-line treatment with only other first-line treatment	3/7 (43%)	2/14 (14%)	0.16
One second-line treatment with only other second-line treatment	0/0 (0%)	0/1 (0%)	—
One second-line treatment with other first-line and other second-line treatment	0/2 (0%)	0/2 (0%)	1.00

Abbreviations: IQR = interquartile range; IVIg = IV immunoglobulin; mRS = modified Rankin score; N = number; PLEX = plasma exchange. Bolded *p* values are statistically significant (*p* < 0.05).

occur with AGO1 Abs.⁷ This study adds that SNN is also the most frequent disorder with AGO1 Abs among the tested peripheral neuropathies. In SNN, AGO1 Abs occur approximately 3 times more frequently than in ONP and even 2 times more frequently than in the non-neurological inflammatory

diseases in which they have been initially identified. While approximately half of patients with SNN with anti-AGO1 Abs had an associated well-identified autoimmune disease, mostly SjS, the other half did not. Approximately one-third of the patients did not have any other biological markers of

Figure 3 Decision Tree of Immunomodulatory Treatment Response



autoimmunity. They represent 8.5% of all patients with SNN without any other marker of autoimmune context. So far, a definite diagnosis of inflammatory SNN cannot be reached in these patients without performing a DRG biopsy, which cannot be recommended.

The clinical pattern of SNN with anti-AGO1 Abs is different from seronegative SNN. In detail, AGO1-associated SNN is more severe, with a higher mRS, more widespread areflexia, and a more severe ENMG pattern. While acute or subacute SNN are frequently autoimmune mediated, 42% of AGO1-positive cases had acute or subacute course in our study. This might be due to the fact that SNN associated with SjS, probably the most typical condition with autoimmune-mediated SNN, frequently have a chronic course.^{17,18}

Because only 2/17 (12%) AGO1 Ab-positive patients with SNN were diagnosed with a cancer, which was not significantly more than among AGO1 Ab-negative patients with SNN (7/101 [7%]), and because 50 Hu Ab-positive patients were seronegative,⁷ we assume that AGO1 Abs are not paraneoplastic.

Although this study was not designed as a therapeutic trial, an important finding is that, despite the low number of evaluated patients, patients with SNN with AGO1 Abs responded more frequently and with a stronger effect to IVIg. When using a decision tree, the frequency of responders to treatment increased from 13/50 (26%) without any further information, over 11/34 (32.4%) when there is an underlying autoimmune context, to 6/9 (66.7%)

when AGO1 Abs are present in addition to an underlying autoimmune context (cf. decision tree in Figure 3). Already in our previous study, several AGO Ab-positive patients with CNS disorder improved with immunomodulatory treatments.⁷ Altogether, these findings suggest that the benefit of AGO Abs as a potential biomarker for treatment decisions in SNN should be studied in a controlled clinical trial or a much larger retrospective or a prospective case-control study using scores that are not dependent on ambulation.

Of interest, patients with anti-AGO1 Abs were more frequently treated by immunomodulatory treatments before testing for anti-AGO Abs (15 such cases). Although most of these cases (11/15 [73%]) had an associated autoimmune context, there were still 4 cases without any documented autoimmune context. Probably the severity of the neuropathy in these patients or the occasional association with an autoimmune disease prompted the clinician to propose an immunomodulatory treatment.

In conclusion, in this retrospective study, SNN is the most frequent neurologic disorder occurring with AGO1 Abs representing 13% of patients with SNN. While approximately half of patients with SNN with AGO1 Abs have an associated autoimmune disease—SjS in most cases—the other half did not. Among patients with SNN without any known context of autoimmunity, 8.5% have AGO1 Abs. AGO1 Ab-positive SNN might represent a more severe and potentially treatable subset of the disease. The significance of

AGO1 Abs in clinical practice needs to be explored on a larger series.

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Disclosure

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