

## RESEARCH REPORT OPEN ACCESS

# Intrathecal Antibody Synthesis in Autoimmune Nodopathy

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## ABSTRACT

**Background:** Autoimmune nodopathy (AN) is caused by autoantibodies targeting the nodes of Ranvier or paranodes. AN frequently affects cranial nerves and spinal nerve roots and may accompany central demyelination, all of which belong to the intrathecal compartment. We aimed to ascertain the frequency of intrathecal antibody synthesis and blood–CSF barrier (BCSFB) dysfunction in AN and their clinical correlates.

**Methods:** We analyzed paired cerebrospinal fluid (CSF) and serum samples from 110 patients with AN, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and Guillain-Barré syndrome (GBS). BCSFB dysfunction and intrathecal total IgG synthesis were assessed using  $Q_{Alb}$ ,  $Q_{IgG-total}$ , and IgG index. Flow cytometry was used to evaluate intrathecal autoantibody synthesis.

**Results:** Compared to CIDP and GBS, AN patients more frequently exhibited BCSFB dysfunction (87.5%) and intrathecal total IgG synthesis (68.8%). Among AN patients with cranial nerve or brain involvement (8/16, 50%), all had either an elevated IgG index ( $n=7$ ) or CSF-specific oligoclonal bands ( $n=1$ ). Intrathecal autoantibody synthesis was confirmed in 2 patients. Notably, both patients initially presented with cranial neuropathies. No CSF-restricted AN autoantibodies were found in the 39 seronegative CIDP and GBS patients.

**Conclusions:** AN exhibits distinct immunopathogenesis compared to CIDP and GBS. Intrathecal synthesis of total IgG is associated with cranial nerve or central nervous system involvement, while that of AN-specific autoantibodies relates to cranial nerve onset diseases.

## 1 | Introduction

Autoimmune nodopathy (AN) is mediated by autoantibodies targeting adhesion proteins at the node of Ranvier and paranodes. It is typically characterized by a subacute onset

of sensory ataxia, distal-dominant weakness, and conduction slowing in nerve conduction study (NCS), hand tremor, and markedly elevated cerebrospinal fluid (CSF) protein levels. In AN, cranial nerves, central nervous system (CNS), and spinal nerve roots are frequently involved. Moreover, recent reports,

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including our own, have described cases that primarily present with cranial nerve or brain lesions [1–4]. These structures commonly correspond to the intrathecal space, where the immune responses can be mediated by autoantibodies produced in the periphery and then crossing the blood-CSF barrier (BCSFB), but they may also be primarily driven by intrathecal immune cells. Despite the distinct clinical phenotype of AN, its potential association with immunopathogenesis remains unexplored.

Here, we analyzed time-matched CSF and sera from patients with AN, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and Guillain-Barre syndrome (GBS), to investigate the frequency and clinical correlates of intrathecal antibody synthesis and BCSFB dysfunction. Additionally, by screening the CSF of seronegative CIDP and GBS patients, we evaluated whether CSF AN antibody testing provides clinical value by enhancing diagnostic yield.

## 2 | Methods

### 2.1 | Study Participants

Between December 2017 and July 2025, sera from patients with suspected CIDP and GBS were collected at 2 neuromuscular centers. Based on routine serum AN antibody testing, patients were categorized as AN or seronegative CIDP or GBS. Demographics, clinical, and laboratory data were obtained via retrospective chart review.

### 2.2 | AN Antibody Assay

Antibody assays were conducted using established methods, as described previously [3, 5]. Seoul National University Hospital verified results from live cell-based flow cytometry with mouse sciatic nerve immunofluorescence, while Severance Hospital used enzyme-linked immunosorbent assay and fixed cell-based immunofluorescence. Detailed protocols are available in [Supplementary Methods](#).

### 2.3 | Determination of BCSFB Dysfunction and Intrathecal Total IgG Synthesis

$Q_{Alb}$ , the albumin quotient, represents the fraction of albumin in CSF relative to that in serum. Under physiological conditions,  $Q_{Alb}$  is age dependent, and its upper normal limit is calculated using the following formula ( $Q_{Alb-lim}$ ). In the presence of BCSFB dysfunction, the high concentration of albumin in serum can diffuse into the CSF, resulting in an elevated  $Q_{Alb}$ . A  $Q_{Alb}$  value exceeding the  $Q_{Alb-lim}$  was considered indicative of significant BCSFB compromise.

$$Q_{Alb} = \frac{\text{CSF albumin (mg/dl)}}{\text{Serum albumin (mg/dl)}}$$

$$Q_{Alb-lim} = \frac{4 + (\text{age}/15)}{10^3}$$

The IgG quotient ( $Q_{IgG-total}$ ) and the IgG index, defined as  $Q_{IgG-total}$  normalized to the  $Q_{Alb}$ , are commonly used indicators of intrathecal total IgG synthesis. An IgG index exceeding 0.6 was considered indicative of a positive intrathecal IgG response.

$$Q_{IgG-total} = \frac{\text{CSF IgG (mg/dl)}}{\text{Serum IgG (mg/dl)}}$$

$$\text{IgG index} = \frac{Q_{IgG-total}}{Q_{Alb}}$$

### 2.4 | Determination of Intrathecal AN-Specific Antibody Synthesis

Time-matched serum and CSF samples from each patient were incubated with Human Embryonic Kidney 293T cells (workflow shown in Figure S1). IgG binding to target antigen-transfected cells, relative to non-transfected ones, was quantified as delta median fluorescence intensity (dMFI) using an Alexa Fluor 647-conjugated anti-human IgG Fc secondary antibody (ThermoFisher). CSF samples were tested at a fixed 1:2 dilution, while serum samples were serially diluted in 7 steps, starting from 1:40 to 1:80, with 2-fold dilutions.

For each patient, a standard curve (x-axis: serum dilution; y-axis: dMFI) was generated from serially diluted serum measurements and fitted to a linear equation with the y-intercept fixed at 0 ( $y=ax$ ). All curves showed excellent linearity ( $R>0.98$ ). This approach uses dMFI as a continuous quantitative measure of antibody binding rather than discrete endpoint titers, enabling interpolation from the curve for higher precision and reproducibility. A linear dilution-dMFI relationship in flow cytometry has been previously demonstrated in AN [6].

The dMFI obtained from the CSF sample ( $y_0$ ) was applied to the standard curve to calculate the corresponding serum dilution ( $y_0/a$ ), which was then multiplied by 2 (reflecting the CSF dilution factor) to yield  $Q_{IgG-specific}$ . This value was divided by  $Q_{IgG-total}$  to yield the Antibody Index (AI), or by the upper normal limit of  $Q_{IgG}$  ( $Q_{IgG-lim}$ ) when  $Q_{IgG-total}$  exceeded this limit, to obtain the corrected AI.  $Q_{IgG-lim}$  was calculated according to Reiber's formula [7]. A corrected AI  $\geq 1.5$  was considered as intrathecal synthesis of AN autoantibodies [8].

$$AI = \frac{Q_{IgG-specific}}{Q_{IgG-total}}$$

$$Q_{IgG-lim} = 0.93\sqrt{Q_{alb}^2 + 6 \times 10^{-6}} - 1.7 \times 10^{-3}$$

$$\text{Corrected AI} = \frac{Q_{IgG-specific}}{Q_{IgG-total}} \quad (\text{if } Q_{IgG-total} < Q_{IgG-lim})$$

$$\frac{Q_{IgG-specific}}{Q_{lim-IgG}} \quad (\text{if } Q_{IgG-total} > Q_{IgG-lim})$$

### 2.5 | Statistical Analysis

Statistical analyses were conducted using R 4.2.1. We used the ANOVA test to assess overall differences in continuous variables

between three groups (AN, CIDP, and GBS), and the Wilcoxon rank sum test for pairwise comparisons. For categorical variables, Fisher's exact test was used. Correlations between continuous variables were analyzed using the Pearson correlation coefficient. A  $p$  value  $< 0.05$  was considered significant.

## 2.6 | Approval and Data Availability

This study was approved by the Institutional Review Boards of Seoul National University Hospital (1704-009-842) and Severance Hospital (4-2021-1328). Written informed consent was obtained from all participants. Additional data is available upon reasonable request.

## 3 | Results

### 3.1 | Participants

Overall study flow is outlined in Figure 1. Among the 315 patient sera analyzed, 22 were identified as AN (NF155,  $n=13$ ; CNTN1,  $n=4$ ; CASPR1,  $n=3$ ; pan-NF,  $n=1$ ; NF186/140,  $n=1$ ). The remaining patients were classified as seronegative CIDP ( $n=227$ ) or GBS ( $n=66$ ).

### 3.2 | $Q_{Alb}$ , $Q_{IgG-total}$ , and IgG Index

$Q_{Alb}$ ,  $Q_{IgG-total}$ , and IgG index were compared between 16 AN, 75 CIDP, and 19 GBS patients (Figure 2A–C, demographics in

Table 1). Significant overall differences were observed among the groups for all 3 parameters ( $p < 0.001$ ).  $Q_{Alb}$  and  $Q_{IgG-total}$  levels were significantly higher in AN patients compared to CIDP and GBS (both  $p < 0.001$ ). The frequency of BCSFB dysfunction was highest in AN (14/16, 87.5%), showing a significant difference compared to CIDP (44/75, 58.7%,  $p=0.043$ ) and GBS (10/19, 52.6%,  $p=0.035$ ). Similarly, the IgG index was significantly higher in AN than in CIDP ( $p=0.011$ ) and GBS ( $p=0.020$ ). The proportion of AN patients (11/16, 68.8%) with intrathecal total IgG synthesis was also significantly higher compared to CIDP (18/75, 24.0%,  $p < 0.001$ ) or GBS (3/19, 15.8%,  $p=0.002$ ). There were no differences in these parameters between CIDP and GBS.

### 3.3 | CSF AN Antibody Positivity and Intrathecal AN Autoantibody Synthesis

Among the 13 patients with AN whose CSF was available, 11 (84.6%) had detectable autoantibodies in the CSF. None of the CSF from 33 CIDP and 6 GBS patients who were seronegative tested positive for AN antibodies.

$Q_{IgG-specific}$  showed a strong positive correlation with CSF white blood cell counts ( $r=0.70$ ,  $p=0.007$ ), but not with CSF protein ( $p=0.19$ ), IgG ( $p=0.38$ ), or albumin levels ( $p=0.30$ ) (Figure 2D–G). There was no significant correlation of CSF white blood cells with intrathecal non-specific IgG synthesis ( $Q_{IgG-total}$ ,  $p=0.50$ ; IgG index,  $p=0.46$ ).  $Q_{IgG-specific}$  levels exceeded the upper normal limit ( $Q_{IgG-lim}$ ) in two patients (cases 1–2, Figure 2H). Corrected AI for both patients was 6.55 (case 1) and 3.58 (case 2), confirming intrathecal AN-specific autoantibody synthesis (Figure 2).

### 3.4 | Clinical Correlates of Intrathecal Antibody Synthesis

Table 2 summarizes the patterns of cranial nerve and CNS involvement and key immunological parameters in our AN cohort (for details, see Table S1). Either clinical or subclinical cranial nerve involvement was identified in 8 out of 16 patients (50%), and two of them had brain MRI lesions resembling multiple sclerosis. Interestingly, all these eight patients exhibited intrathecal total IgG synthesis or, as in case 11, CSF-specific oligoclonal bands (Figure S2). Intrathecal AN-specific autoantibody synthesis in case 11 could not be assessed due to the absence of an available CSF sample. Cases 1 (CN IV), 2 (CN II), and 4 (CN II) initially presented with cranial nerve symptoms prior to limb involvement. Excluding case 4, for whom the CSF sample archived was unavailable, the remaining two showed positive intrathecal autoantibody synthesis.

### 3.5 | Two Cases With Intrathecal Autoantibody Synthesis

Clinical characteristics of two cases with intrathecal autoantibody synthesis are summarized in Table 3. Case 1 is a 68-year-old diabetic male with anti-CNTN1 IgG4 antibodies who initially developed right superior oblique palsy, followed by a subacute onset of sensory ataxia, ascending paresthesia and numbness, and distal weakness. He also had nephrotic

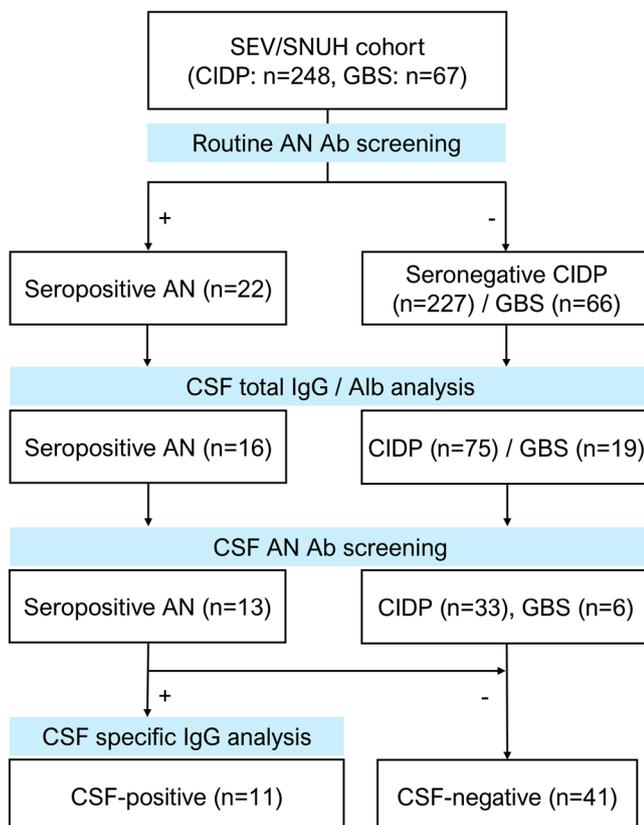
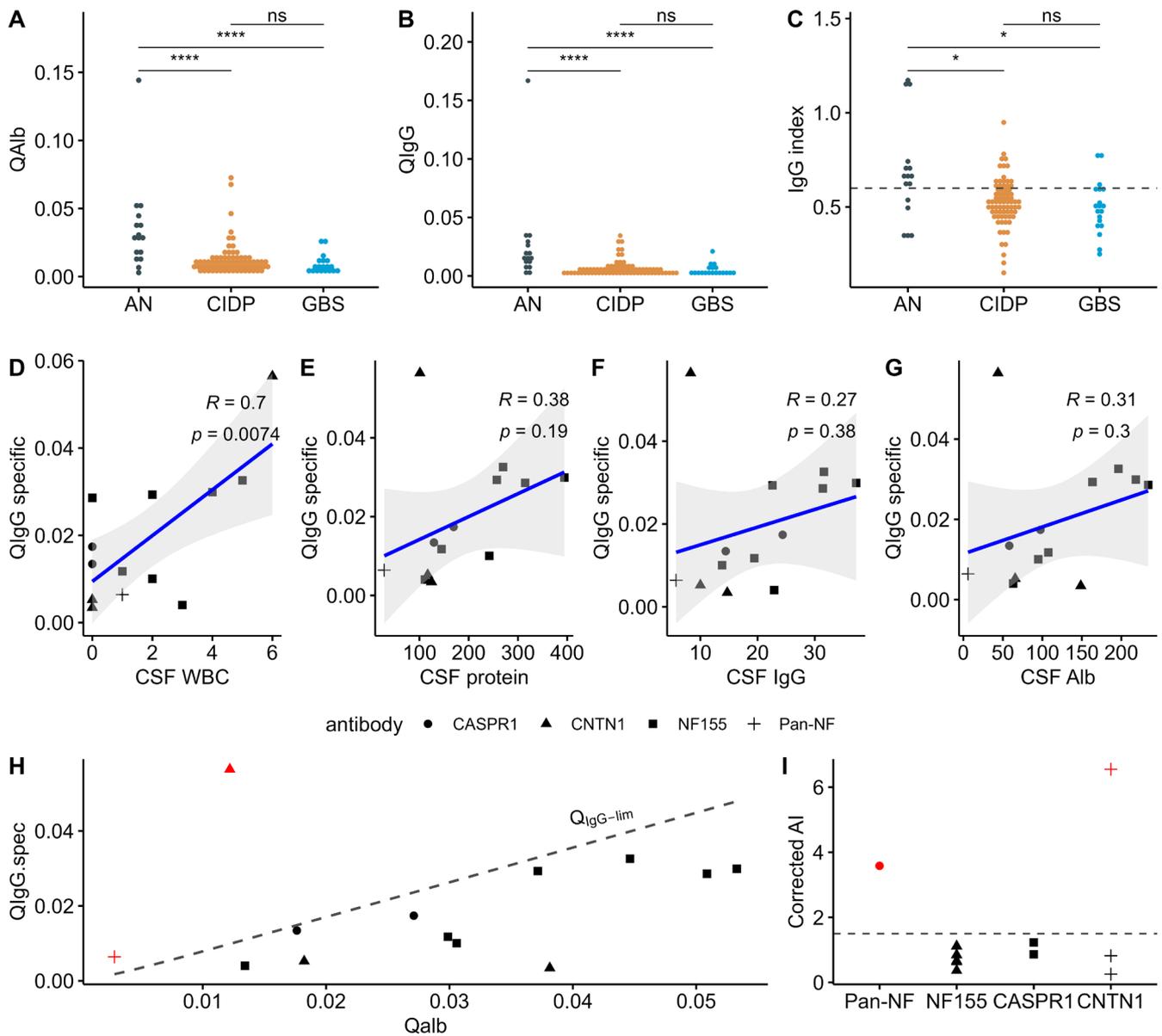


FIGURE 1 | Overall study flow.



**FIGURE 2** | Key findings in this study. (A–C)  $Q_{alb}$ ,  $Q_{lgG-total}$ , and IgG index values across diagnostic groups. (D–G) Correlation between  $Q_{lgG-specific}$  and CSF parameters in AN patients. (H) Reibergram illustrating intrathecal AN-specific autoantibody synthesis. (I) Corrected AI values in AN patients.

**TABLE 1** | Baseline characteristics of included patients.

	AN	CIDP	GBS	P
Number of subjects	16	75	19	ns
Female, <i>n</i> (%)	7 (44%)	28 (37%)	5 (26%)	ns
Age (yr), mean (SD)	48 (20)	56 (18)	50 (21)	ns

syndrome, and electrophysiological studies confirmed bilateral facial nerve involvement and “demyelinating” polyneuropathy. Case 2 is a 40-year-old female with IgG1 isotype pan-NF antibodies, whose first episode began with bilateral optic neuritis, followed by distal paresthesia, numbness, sensory ataxia, and concurrent nephrotic syndrome. She has a medical history of epilepsy and Sjögren’s syndrome. The second episode presented as more severe weakness (motor grade 3–4), with right facial

palsy and hearing loss. Electrophysiological studies revealed numerous conduction blocks, as well as blink reflex abnormalities suggesting facial efferent deficits. Both patients had favorable outcomes; Case 1 completely recovered to IVMP followed by mycophenolate mofetil and prednisone, while Case 2 showed a good response to IVIG.

#### 4 | Discussion

We found that patients with AN exhibit more prominent BCSFB dysfunction and intrathecal total IgG synthesis compared with CIDP and GBS. Notably, intrathecal IgG synthesis was associated with clinical or subclinical involvement of cranial nerves and the brain. Most seropositive AN patients also had detectable autoantibodies in their CSF, and in two cases, positive intrathecal autoantibody synthesis coincided with cranial nerve onset.

**TABLE 2** | Summary of the clinical features, intrathecal antibody synthesis, and BCSFB dysfunction in the AN cohort.

No.	Antibody	Cranial nerve or CNS involvement		Intrathecal IgG synthesis		
		Symptom/Sign	EDX/MRI	AN IgG	Total IgG	BCSFB
1	CNTN1	IV*, VII	VII	+	+	+
2	Pan-NF	II*, VII	VII	+	+	-
3	NF155	VII	VII, VIII, Brain	-	+	+
4	NF155	II	II, V, VII	NA	+	+
5	NF155	-	III, V, XI	-	+	+
6	NF155	-	VIII, Brain	-	+	+
7	CASPR1	-	VII, VIII	-	+	+
8	CASPR1	-	-	-	+	+
9	NF155	-	-	-	+	+
10	NF155	-	NA	-	+	+
11	NF186	VII, IX-X	VII	NA	- (CSF OCB +)	-
12	NF155	-	NA	NA	-	+
13	NF155	-	NA	-	-	+
14	NF155	-	-	-	+	+
15	CNTN1	-	-	-	-	+
16	CNTN1	-	NA	-	-	+

Note: Asterisks (\*) indicate the initial manifestation.

Abbreviations: BCSFB, Blood-CSF barrier dysfunction; CASPR1, contactin-associated protein 1; CNS, central nervous system; CNTN1, contactin-1; EDX, electrodiagnosis; MRI, magnetic resonance imaging; NF, neurofascin; OCB, oligoclonal band.

These findings provide novel insights into the relationship between immunopathogenic features and clinical manifestations in AN.

The cranial nerves or the CNS are frequently affected in AN [2]. Previous cohort studies have reported cranial nerve involvement in 55% of anti-NF155, 30% of anti-CNTN1, 40% of anti-CASPR1, and 81.8 to 100% of anti-pan-NF associated AN cases [9–13]. In our cohort, 5 out of 16 patients (33.3%) exhibited symptoms and clinical signs of cranial involvement, and an additional 3 patients (20%) showed subclinical abnormalities on electrodiagnosis and/or neuroimaging. Of these 8 patients, 7 had an elevated IgG index, and the remaining patient exhibited CSF-specific oligoclonal bands. These findings provide a novel mechanistic insight that intrathecal immune response frequently occurs in AN and may contribute to neural involvement in these regions.

Among the 3 patients whose initial manifestation was cranial neuropathy, CSF samples were available for 2, both of whom demonstrated positive intrathecal autoantibody synthesis. A quantitative marker of intrathecal autoantibody synthesis,  $Q_{\text{IgG-specific}}$ , as well as AI, correlated positively with CSF white blood cell counts. These findings raise the possibility that, while in many patients autoimmunity originates from the periphery and enters the intrathecal space via a leaky BCSFB, in some cases immune cells within the CSF may themselves secrete autoantibodies to drive the disease process. Recently, AN cases have been reported with CNS

symptoms such as memory impairment, involuntary movements [4], or cerebellar dysarthria [1]. It would be of interest to investigate whether intrathecal antibody synthesis is also present in these patients.

Myelin oligodendrocyte glycoprotein (MOG) autoantibodies have recently been detected exclusively in the CSF of patients with CNS demyelinating diseases, particularly in those with extensive brain or spinal cord lesions, underscoring the importance of CSF testing for MOG antibodies [8, 14, 15]. In this context, we screened CSF samples from 39 GBS or CIDP patients to assess the potential diagnostic value of CSF testing for AN antibody, but no positive cases were identified among these seronegative cases. This suggests that the clinical utility of CSF AN antibody screening may be limited, at least in patients presenting with typical polyneuropathy, although confirmation in larger cohorts is warranted.

Nearly all our AN patients exhibited markedly elevated  $Q_{\text{Alb}}$  levels, significantly higher than those with CIDP and GBS. This is consistent with previous studies reporting highly elevated CSF protein levels and pronounced root hypertrophy in AN [6]. The BCSFB consists of fenestrated capillaries and epithelial lining joined by tight junctions (TJs). In CIDP, T-cell-secreted proinflammatory cytokines and chemokines, such as matrix metalloproteinase, disrupt BCSFB by down-regulating barrier proteins including claudin-5 [16, 17]. How IgG4 isotype-predominant autoantibodies in AN compromise the barrier remains an open question that warrants future

**TABLE 3** | Clinical characteristics of 2 patients with intrathecal AN autoantibody synthesis.

	Case 1	Case 2	
Antibody (subclass)	CNTN1 (IgG4 > IgG1)	Pan-NF (IgG1)	
Sex/Age	M/68	F/40	
Clinical presentation	First episode (no relapse thereafter)	First episode	Second episode (5 months later)
	Subacute (Nadir at week 8)	Acute (Nadir at week 4)	Chronic (Nadir at month 3)
Neurological examination	Vertical diplopia (D1) Paresthesia, numbness (feet, fingertip, flank) (D20-30) Sensory ataxia, hand tremor, ageusia, dysarthria, facial diplegia, leg weakness (D50-60)	Bilateral visual acuity change (D1) Paresthesia and numbness (feet, hands and then to leg) (D15) Sensory ataxia (D20)	Weakness: right hand (D1) → both legs (D4) → both arms (D8) Right facial palsy & hearing loss (D12)
	Right CN IV palsy Hyporeflexia Positive Romberg test Decreased proprioception and vibration	No RAPD Hyporeflexia Decreased proprioception and vibration Intact motor power	Right peripheral type facial palsy Symmetric proximal and distal weakness (grade 3~4) Hyporeflexia Intact sensation (light touch, pinprick, temperature, vibration, position)
INCAT at nadir	4	4	9
MRCSS at nadir	56/60	80/80	56/80
Comorbidity	Diabetes Nephrotic syndrome	Generalized Epilepsy (30 years ago) Sjogren's syndrome (5 years ago) Nephrotic syndrome (FSGS)	
Limb NCS (EAN/PNS criteria)	Definite (DML & F: 2 nerves, TD & DUR: 1 nerve)	Absent H-reflexes but otherwise normal	Definite (CB: 4 nerves, F: 2 nerves)
Facial NCS	Prolonged DML (bilateral)	ND	Normal
Blink reflex	Right: absent iR1 Left: prolonged iR1	ND	Right: absent iR1, prolonged iR2 Left: absent cR2
IgG index	0.71	NA	1.43
Brain MRI	Unremarkable	ND	Unremarkable
Spinal cord MRI	Unremarkable	ND	Unremarkable
Treatment	IVMP → MMF/Pd : good response	IVMP: no response IVIG: good response	IVMP, PE: no response IVIG: good response

Abbreviations: c, Contralateral; CNTN1, contactin-1; D, day; DML, distal motor latency; DUR, distal CMAP duration; EAN/PNS, European Academy of Neurology/Peripheral Nerve Society; F, female; FSGS, focal segmental glomerulosclerosis; i, ipsilateral; INCAT, inflammatory neuropathy cause and treatment; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; M, male; MMF, mycophenolate mofetil; MRCSS, medical research council sum score; NCS, nerve conduction study; NF, neurofascin; Pd, prednisolone; TD, temporal dispersion.

investigation [18]. It may be mediated by less dominant IgG1-3 autoantibodies, result from potential molecular mimicry between AN antigens and BCSFB TJs, or represent a prerequisite for the development of AN.

In conclusion, our study provides novel insights into the intrathecal pathophysiology of AN. Compared to CIDP and GBS, AN more frequently exhibits BCSFB dysfunction and intrathecal IgG synthesis. Intrathecal synthesis of the total IgG and

AN-specific autoantibodies is associated with cranial nerve involvement and cranial nerve onset, respectively. Further research is needed to clarify the role of CSF AN antibody testing and to elucidate the mechanisms underlying BCSFB dysfunction.

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### Ethics Statement

This study was approved by the Institutional Review Boards of Seoul National University Hospital (1704–009-842) and Severance Hospital (4–2021-1328). Written informed consent was obtained from all participants.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supplementary Figure 1:** Flow cytometric assay for quantitative assessment of intrathecal AN-specific autoantibody synthesis. Supplementary Figure 2. CSF-specific oligoclonal bands in Case 11 (indicated as 499). White and grey arrowheads represent clear and faint bands, respectively, that are present only in the CSF and absent in the serum. The two columns on the right show results from a negative control and positive control subject, respectively. Supplementary Table 1. Clinical characteristics and detailed immunological parameters of our AN cohort.