

# Diabetes Mellitus Is a Possible Risk Factor for Nodo-paranodopathy With Antiparanodal Autoantibodies

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## Abstract

### Background and Objectives

Nodo-paranodopathies are peripheral neuropathies with dysfunction of the node of Ranvier. Affected patients who are seropositive for antibodies against adhesion molecules like contactin-1 and neurofascin show distinct clinical features and a disruption of the paranodal complex. An axoglial dysjunction is also a characteristic finding of diabetic neuropathy. Here, we aim to investigate a possible association of antibody-mediated nodo-paranodopathy and diabetes mellitus (DM).

### Methods

We retrospectively analyzed clinical data of 227 patients with chronic inflammatory demyelinating polyradiculoneuropathy and Guillain-Barré syndrome from multiple centers in Germany who had undergone diagnostic testing for antiparanodal antibodies targeting neurofascin-155, pan-neurofascin, contactin-1-associated protein 1, and contactin-1. To study possible direct pathogenic effects of antiparanodal antibodies, we performed immunofluorescence binding assays on human pancreatic tissue sections.

### Results

The frequency of DM was 33.3% in seropositive patients and thus higher compared with seronegative patients (14.1%, OR = 3.04, 95% CI = 1.31–6.80). The relative risk of DM in seropositive patients was 3.4-fold higher compared with the general German population. Seropositive patients with DM most frequently harbored anti-contactin-1 antibodies and had higher antibody titers than seropositive patients without DM. The diagnosis of DM preceded the onset of neuropathy in seropositive patients. No immunoreactivity of antiparanodal antibodies against pancreatic tissue was detected.

### Discussion

We report an association of nodo-paranodopathy and DM. Our results suggest that DM may be a potential risk factor for predisposing to developing nodo-paranodopathy and argue against DM being induced by the autoantibodies. Our findings set the basis for further research investigating underlying immunopathogenetic connections.

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## Glossary

**Caspr-1** = contactin-1–associated protein 1; **CIDP** = chronic inflammatory demyelinating polyradiculoneuropathy; **DM** = diabetes mellitus; **GAD** = glutamate decarboxylase; **GBS** = Guillain-Barré syndrome; **HbA1c** = hemoglobin A1c; **Ig** = immunoglobulin; **PE** = plasma exchange.

In the past decade, nodo-paranodopathy has emerged as a new concept in the spectrum of peripheral neuropathies. In this context, immunoglobulin (Ig) G autoantibodies against cell adhesion molecules like contactin-1, contactin-1–associated protein 1 (Caspr-1), and neurofascin isoforms have been described.<sup>1</sup> These proteins constitute the axoglial junction at the paranodal region of the node of Ranvier and are essential for saltatory conduction.<sup>2</sup> Antiparanodal antibodies impair nodal integrity and function.<sup>1</sup> The primary trigger of autoimmunity, however, has still not been identified. The patients show a distinct phenotype, which frequently manifests with an acute onset, severe sensorimotor neuropathy, sensory ataxia, tremor, and neuropathic pain.<sup>1,3,4</sup> The IgG subclass may influence the course of disease and response to therapy.<sup>1,5</sup> Antiparanodal antibodies thus are novel biomarkers with direct implications for monitoring and treatment.

An axoglial dysjunction at the node of Ranvier also occurs in diabetic neuropathy, possibly exposing antigens to the immune response.<sup>6</sup> Diabetes mellitus (DM) has been discussed controversially as a risk factor in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and has lately been confirmed in multicenter studies.<sup>7</sup> We previously described DM as a comorbidity in patients with antiparanodal antibodies.<sup>5</sup> However, little is known about the frequency of DM in nodo-paranodopathy. We therefore investigated a possible clinical association of DM and nodo-paranodopathy in a large cohort of patients with immune-mediated neuropathies.

## Methods

### Patients and Clinical Data

We included 156 patients with CIDP fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society criteria from 2010<sup>8</sup> (n = 129 definite, n = 19 probable, and n = 8 possible) and 71 patients with Guillain-Barré syndrome (GBS) according to the Brighton criteria<sup>9</sup> (n = 50 level 1, n = 11 level 2, n = 2 level 3, and n = 8 level 4) whose sera had been collected between 2005 and 2021 at multiple centers in Germany for routine diagnostic workup purposes and who had undergone antiparanodal autoantibody testing via ELISA and confirmation with cell-based assay at the University Hospital of Würzburg as previously described.<sup>5,10</sup> Clinical data were collected retrospectively. Patients with/without antiparanodal antibodies are further referred to as seropositive/seronegative.

### Standard Protocol Approvals, Registrations, and Patient Consents

The Ethics Committee of the Medical Faculty, University of Würzburg, approved the study. The patients whose sera were used in the analysis had given written informed consent.

### Statistical Analysis

Descriptive and statistical data analysis were performed using SPSS Statistics version 28.0 (IBM, Armonk, NY) and Prism V9.3.0 (GraphPad Software, San Diego, CA), including the d'Agostino Pearson test for normality distribution and the  $\chi^2$  test, Student's *t* test, Mann-Whitney test, and Spearman correlation coefficient.

### Immunofluorescence Staining on Human Normal Pancreatic Tissue

Five-micrometer sections of paraffine-embedded pancreatic tissue from the Department of Pathology of the University of Würzburg were deparaffinized, rehydrated, and steamed in 10 mM citrate buffer. The slides were washed and blocked. Afterwards, double immunofluorescence staining was performed with rabbit-anti-synaptophysin (AB9272; Merck, Darmstadt, Germany) as one primary antibody and either serum of a patient with anti-glutamate decarboxylase (GAD)-associated DM type 1, or 2 seronegative patients, or 2 seropositive patients of each paranodal target antigen or commercial antiparanodal antibodies (polyclonal chicken anti-pan-neurofascin 1:1,000, AF3235; R&D Systems, Minneapolis, MN; monoclonal mouse anti-Caspr-1 1:100, Sc-373777 [E-8]; Santa Cruz Biotechnology, Dallas, TX; polyclonal goat anti-contactin-1 1:200, ab191285; Abcam, Cambridge, United Kingdom) as the other primary antibodies. After a secondary antibody incubation (Jackson Immuno Research, West Grove, PA), sections were viewed with a fluorescence microscope (Zeiss Axiovert 200M; Zeiss, Oberkochen, Germany).

### Data Availability

Anonymized data will be made available on request from any qualified investigator.

## Results

### Frequencies of Antiparanodal Antibodies in the Cohort

Our cohort included 191 (84.1%) seronegative patients and 36 (15.9%) patients IgG seropositive for antiparanodal antibodies. The predominant antibody subclass was IgG4 in 18/36 patients, IgG3 in 12/36 patients, IgG2 in 3/36 patients, IgG1 in 1/36 patients, and not determinable in 2/36 patients. Table 1 displays serostatus and demographic data.

### Increase in Frequency of DM in Seropositive Patients

A disorder of glucose metabolism was diagnosed in 17.2% of the entire cohort (39/227; according to the World Health Organization criteria<sup>11</sup>: n = 2 DM type 1; n = 33 DM type 2; n = 4

**Table 1** Serostatus, Diagnoses, and Demographic Data of the Cohort

	Total, N (%)	CIDP, n (%)	GBS, n (%)	Age, mean (SD)
Seronegative	191 (84.1)	126 (55.5)	65 (28.6)	58.09 (14.6)
Seropositive	36 (15.9)	30 (13.2)	6 (2.6)	57.51 (16.5)
Neurofascin-155	8 (3.5)	8 (3.5)	0 (0.0)	48.00 (21.5)
Pan-neurofascin	10 (4.4)	9 (4.0)	1 (0.4)	60.00 (15.5)
Contactin-1	10 (4.4)	8 (3.5)	2 (0.9)	63.70 (13.6)
Caspr-1	6 (2.6)	4 (1.8)	2 (0.9)	53.67 (16.2)
Caspr-1/contactin-1	2 (0.9)	1 (0.4)	1 (0.4)	63.50 (6.4)
Σ	227 (100)	156 (68.7)	71 (31.3)	58.00 (14.9)

Abbreviations: Caspr = contactin-1-associated protein; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; GBS = Guillain-Barré syndrome. Numbers represent the number of patients included in the study. Frequencies are displayed in brackets as percentage of the total cohort. Mean age is shown with SD in brackets.

impaired glucose tolerance). In seropositive patients, the frequency of DM was 33.3% and thus significantly higher compared with seronegative patients (14.1%), especially in anti-contactin-1-seropositive patients (58.3%; Table 2 and Figure, A). Performing a subanalysis in the CIDP and GBS cohort, we could

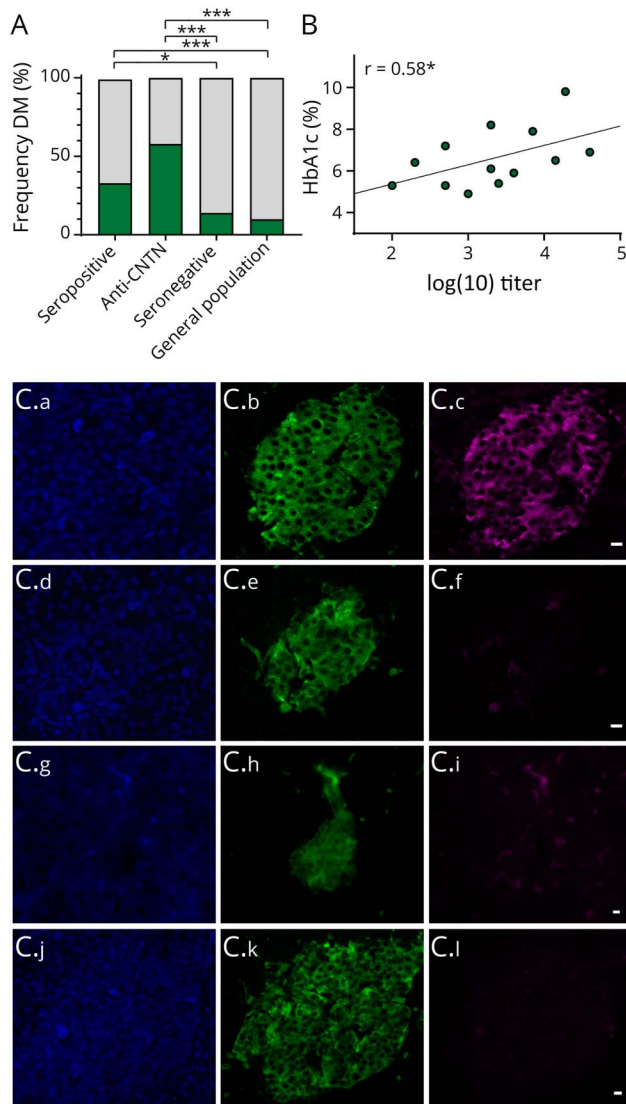
show a significant increase in the frequency of DM in the CIDP subcohort (seropositive 33.3% vs seronegative 15.1%). In the GBS subcohort, we found a similar tendency that did not reach statistical significance (Table 2). Although patients with DM were significantly older than patients without DM in the total

**Table 2** Results of Statistical Testing

	Seropositive	Seronegative	p Value	OR (95% CI)
<b>Frequency of DM, n (%)</b>				
Total cohort, all antiparanodal antibodies	12/36 (33.3)	27/191 (14.1)	<b>0.014<sup>a</sup></b>	3.04 (1.31 to 6.80)
CIDP subcohort	10/30 (33.3)	19/126 (15.1)	<b>0.034<sup>a</sup></b>	2.82 (1.14 to 6.94)
GBS subcohort	2/6 (33.3)	8/65 (12.3)	0.197 <sup>a</sup>	3.56 (0.56 to 22.70)
Anti-contactin-1 subcohort	7/12 (58.3)	27/191 (14.1)	<b>&lt;0.001<sup>a</sup></b>	8.50 (2.64 to 25.42)
Anti-neurofascin subcohort	4/18 (22.2)	27/191 (14.1)	0.316 <sup>a</sup>	1.74 (0.53 to 5.67)
Anti-Caspr-1 subcohort	3/8 (37.5)	27/191 (14.1)	0.102 <sup>a</sup>	3.64 (0.82 to 16.14)
Subcohort of all patients >age 60 y	8/20 (40.0)	18/98 (18.4)	<b>0.042<sup>a</sup></b>	2.96 (1.01 to 7.65)
Subcohort of anti-contactin-1 >age 60 y	5/9 (55.0)	18/98 (18.4)	<b>0.021<sup>a</sup></b>	5.56 (1.36 to 22.77)
Patients with documented HbA1c only	11/19 (57.9)	22/84 (26.2)	<b>0.013<sup>a</sup></b>	3.88 (1.41 to 11.41)
Female-to-male ratio, n (%)	11/25 (30.5)	43/148 (22.5)	0.294 <sup>a</sup>	0.66 (0.31 to 1.44)
<b>Mean age (SD)</b>				
Total cohort	57.50 (16.68)	58.09 (14.60)	0.828 <sup>b</sup>	-4.77 to 5.94
DM subcohort	65.07 (11.79)	64.25 (9.40)	0.832 <sup>b</sup>	-7.00 to 8.65
<b>Median HbA1c</b>				
Total cohort	5.50	5.70	0.821 <sup>c</sup>	
DM subcohort	6.50	6.45	0.985 <sup>c</sup>	

Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; DM = diabetes mellitus; HbA1c = hemoglobin A1c. Frequencies (n/total, with percentage in brackets) in the main analysis and subanalysis, female-to-male ratio, and mean/median values (including SD in brackets) of age and HbA1c are displayed in seropositive and seronegative patients of the cohort. Results of statistical tests are displayed in the last 2 rows. Results are considered statistically significant at  $p < 0.05$  (<sup>a</sup> $\chi^2$  test, <sup>b</sup>Student's  $t$  test, and <sup>c</sup>Mann-Whitney test). OR is displayed with 95% CI.

**Figure** Frequency of DM and Immunofluorescence Stainings on Pancreatic Tissue



(A) Frequency of diabetes mellitus is significantly elevated in patients seropositive for antiparanodal antibodies (33.3%) compared with seronegative patients (14.1%,  $p = 0.014$ ) and with the general German population (9.9%,  $p < 0.001$ ), especially in anti-contactin-1-seropositive patients (58.3% vs 14.1% in seronegative,  $p < 0.001$  and 9.9% in the German population,  $p < 0.001$ ). Significance levels are marked with asterisks: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . (B) In seropositive patients not having received corticosteroid treatment within the last 28 days and who were therapy naive to rituximab, HbA1c levels (y-axis, %) were determined in 14 patients at the time point of serum withdrawal and correlated significantly with the autoantibody titer, displayed on a logarithmic scale ( $r = 0.58$ ,  $p = 0.029$ ). (C.a-l) Photomicrographs show human pancreatic normal tissue sections with nucleus staining (DAPI) shown in blue (C.a, C.d, C.g, and C.j) and double staining with synaptophysin as marker for the islets of Langerhans (displayed in green, C.b, C.e, C.h, and C.k) and serum or antiparanodal antibodies (displayed in magenta, C.c, C.f, C.i, and C.l). Serum of a patient with CIDP and DM type 1 with GAD antibodies binds to  $\beta$  cells in pancreatic islets of Langerhans (C.a-c), whereas serum of a patient with anti-contactin-1 antibodies (C.d-f) and commercial goat anti-contactin-1 (C.g-i) and commercial chicken anti-pan-neurofascin (C.j-l) do not show any binding. Photomicrographs of binding of the other patients' sera or commercial antibodies tested in the assay are not shown. Scale bar = 10  $\mu$ m. CNTN = contactin-1; DAPI = 4',6-diamidino-2-phenylindole; DM = diabetes mellitus; HbA1c = hemoglobin A1c.

cohort (64.82 vs 56.57,  $p < 0.002$ ), the mean age and female-to-male ratio did not differ between seropositive and seronegative patients (Table 2). In patients aged  $>60$  years, the frequency of DM was still significantly elevated in seropositive vs seronegative patients.

Treatment with plasma exchange (PE), IVIg, and corticosteroids was assessed retrospectively in the last 28 days before serum withdrawal and rituximab or further immunosuppressive treatment until 1 year before the withdrawal. There were no significant differences in previous PE, IVIg, and corticosteroid treatment in patients with and without DM (PE 2/12 [16.6%] vs 2/24 [8.3%],  $p = 0.59$ ; IVIg 2/12 [16.7%] vs 8/24 [33.3%],  $p = 0.44$ ; corticosteroids 1/12 [8.3%] vs 13/24 [54.2%],  $p = 0.22$ ). Nevertheless, patients having received corticosteroids ( $n = 8$ ) were excluded from the titer analysis to avoid bias. They were mainly found in the nondiabetic group because corticosteroids are often avoided in patients with diabetes. Furthermore, corticosteroid treatment influences total IgG levels until 2–4 weeks after application.<sup>12</sup> None of the patients had received rituximab treatment or further immunosuppressive treatment before antibody testing. Titers in the remaining 28 seropositive patients ranged from 1:100 to 1:40,000 and were significantly higher in patients with DM than without DM (median of 1:2,000 vs 1:500,  $p = 0.035$ ).

Hemoglobin A1c (HbA1c) was determined at the onset of neurologic symptoms in 103 (45.4%) patients. The maximum HbA1c values were significantly higher in patients with DM compared with individuals without diabetes (mean of 6.5 vs 5.5,  $p < 0.001$ ), but did not differ in seropositive and seronegative patients with DM (Table 2). We performed a sub-analysis of the frequency of DM with patients whose HbA1c values were measured and documented at the time point of serologic testing. Here, the frequency of DM stayed significantly higher in seropositive vs seronegative patients (Table 2). Furthermore, HbA1c levels correlated significantly with the autoantibody titer ( $r = 0.584$ ,  $p = 0.029$ ; Figure, B) in  $n = 14$  patients whose titer and HbA1c were assessed simultaneously and considered in the analysis (see above).

In all seropositive patients, the diagnosis of DM preceded the acute onset of nodo-paranodopathy without any close temporal connection. In 2/12 seropositive patients, the time point of diagnosis was documented  $>10$  years before the onset of neurologic symptoms. In the other patients, the exact time point of DM diagnosis was not documented, but all patients carried an established diagnosis of diabetes before the onset of nodo-paranodopathy, and 10/12 patients had received long-term antidiabetic treatment.

DM type 2 occurred independently of the predominant IgG subclass: in 1/1 (100%) patients with predominant IgG1, in 1/3 (33%) patients with predominant IgG2, in 3/12 (25%) patients with predominant IgG3, and in 6/18 (33.3%)



patients with predominant IgG4. In 1 patient, DM type 1 was diagnosed 15 years before the onset of nodo-paranodopathy. This patient had reported normal total IgG4 levels 3 years before the onset of nodo-paranodopathy. At the onset of neurologic symptoms, IgG4 antibodies against pan-neurofascin were detected.

### Relative Risks and Comparison to Previous Studies

The relative risk of DM compared with the general German population according to health insurance data<sup>13</sup> was 3.4-fold higher in seropositive patients (33.3% vs 9.9%,  $p < 0.001$ ; Figure, A) and 1.88-fold higher in our entire CIDP cohort (18.6% vs 9.9%,  $p < 0.01$ ). The frequency of DM in our total CIDP cohort did not differ significantly from previously described European CIDP cohorts<sup>7</sup> ( $n = 29/156$ , 18.6% vs  $n = 48/257$ , 18.7%,  $p > 0.999$ ).

### No Binding of Antiparanodal Antibodies to Pancreatic $\beta$ -Cell Islets

On normal pancreatic tissue sections, commercial antibodies against synaptophysin and patient anti-GAD antibodies as positive controls bound specifically to insulin-producing  $\beta$  cells in the Langerhans islets (Figure, C). Neither the commercial antibodies against nodo-paranodal antigens nor the patient sera with anti-contactin-1, anti-Caspr-1, and anti-neurofascin antibodies showed any binding to  $\beta$  cells (Figure, C representatively illustrates binding assays with serum and commercial anti-contactin-1 and commercial anti-pan-neurofascin, other data not shown).

## Discussion

We report an association of antiparanodal antibodies and DM and identify DM as a possible risk factor for developing nodo-paranodopathy. An approximately 2-fold increase of the relative risk of DM compared with the general population has been described in European cohorts of CIDP<sup>7</sup> and was confirmed by our data. Furthermore, we detected a 3.4-fold increase of the relative risk in antibody-mediated CIDP, supporting the notion of humoral immunity playing a major role in the association of CIDP and DM.

As we did not detect any binding of antiparanodal antibodies to pancreatic tissue, our data suggest that immunogenic target epitopes of proteins recognized by the antibodies are likely not to be present in the pancreas. Thus, antiparanodal antibodies do probably not have a direct pathogenic effect on pancreatic  $\beta$  cells. This hypothesis is supported by the fact that in the patient with DM type 1, diagnosis preceded the onset of IgG4-related neurologic disease. We therefore hypothesize that nodo-paranodopathy may be associated to a preexisting DM or hyperglycemic condition.

A diabetes-related blood-nerve barrier dysfunction and upregulation of proinflammatory cytokines have been

suggested as promoting factors for CIDP.<sup>6,14</sup> DM leads to a disruption of the paranodal junction.<sup>6,15</sup> This could expose paranodal targets like contactin-1 to the adaptive immune response, supported by our finding of higher autoantibody titers in patients with DM and the correlation of HbA1c levels with the autoantibody titers. Especially IgG4-related disease occurs after chronic antigen exposure<sup>16</sup> and might therefore be triggered by diabetes-associated long-term pathologic structural changes. Furthermore, the disruption of paranodal architecture could facilitate the access of the autoantibodies to the paranodal complex, which is protected by the myelin barrier under physiologic conditions.<sup>17</sup> We hypothesize that these factors increase the risk of developing nodo-paranodopathy.

Patients with IgG4-related nodo-paranodopathy respond well to antibody depletion with rituximab, as recommended in the European Federation of Neurological Societies/Peripheral Nerve Society guidelines.<sup>18</sup> Whether additional treatment should be adapted depending on the presence of DM needs to be addressed in further studies.

A possible bias when comparing frequencies in cohorts with the general population prevalence rates in this and other studies<sup>7</sup> is the age-dependent increase of the prevalence of DM. Therefore, we used age-matched controls in our cohort and considered age-dependent effects by a subanalysis of patients aged  $>60$  years, thus reducing the risk of age as a possible confounder for our cohort data.

Within seropositive patients, we found a strong association of DM and anti-contactin-1. These patients are older than patients with antibodies targeting neurofascin-155.<sup>4</sup> We therefore hypothesize that in the elderly, DM and its associated conditions may potentially predispose to developing nodo-paranodopathy. In the young, however, other triggers still need to be investigated.

In a subanalysis, we found the frequency of DM only to be increased in our CIDP cohort. In our GBS cohort, we found a similar tendency, but studies with larger GBS cohorts are needed to study an association. Furthermore, the frequency of antiparanodal antibodies in our cohort is higher than previously reported prevalences,<sup>1</sup> possibly due to a selection bias as a national center for antibody diagnostics. Therefore, given the low prevalence of antiparanodal antibodies and the retrospective character of this explorative analysis, larger international multicenter studies are needed to address the role of humoral immunity with focus on antiparanodal antibodies and DM in CIDP and GBS and investigate the role of DM and its associated conditions in paranodopathy using multivariate models. Following experimental studies may elucidate the exact pathoimmunologic mechanisms.

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## Disclosure

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<b>Luise Appeltshauer, MD</b>	University Hospital of Würzburg, Germany	Study design and conception; data acquisition, analysis, and interpretation; drafting of the first version of the manuscript; and revision of the manuscript for intellectual content

## Appendix (continued)

Name	Location	Contribution
<b>Julia Messinger</b>	University Hospital of Würzburg, Germany	Data acquisition and revision of the manuscript for content
<b>Katharina Starz</b>	University Hospital of Würzburg, Germany	Data acquisition and revision of the manuscript for content
<b>David Heinrich</b>	University Hospital of Würzburg, Germany	Data acquisition and revision of the manuscript for content
<b>Anna-Michelle Brunder</b>	University Hospital of Würzburg, Germany	Data acquisition and revision of the manuscript for content
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## Appendix (continued)

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<b>Kathrin Doppler, MD</b>	University Hospital of Würzburg, Germany	Study design and conception; data acquisition; and revision of the manuscript for content

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