Appendix e-1 Clinical data and course of disease in seropositive patients

subcohort	GBS		A-CIDP		
patient number	**patient 1**	**patient 2**	**patient 3**	**patient 4**	**patient 5**
serostatus at baseline	anti-Caspr-1 IgG3 1:100	anti-Caspr-1/ anti-contactin-1, IgG2 1:200	anti-contactin-1 IgG2/4 1:30,000	anti-Caspr-1/ anti-contactin-1, IgG3 1:500	anti-Caspr-1, IgG3 1:100
course of disease	monophasic	monophasic	chronic progressive	relapsing remitting	relapsing remitting
age	61	59	75	68	47
sex	female	female	female	female	male
disease duration at first assessment (days)	10	2	14	7	45
duration until peak of symptoms (days)	16	10	24	7	90
Δ time (months) between 1st serum assessment and follow-up sampling	n.a.	55	n.a.	120	2
Δ time (months) of clinical follow-up	1	55	2	163	77
antecedent infection	none	none	none	n.d.a.	vaccination against hepatitis A/B respiratory infection
relevant comorbidities	none	Diabetes Mellitus type 2	Diabetes Mellitus type 2 renal insufficiency	Diabetes Mellitus type 2	cervical (C3/4) and lumbar (L5/S1) herniated discs
first manifestation	motor	sensorimotor	sensorimotor	sensorimotor	sensory
distribution	proximal symmetrical arms > legs	distal and proximal asymmetrical arms = legs	distal symmetrical arms = legs	distal symmetrical arms = legs	distal symmetrical arms = legs
motor symptoms at onset	severe tetraparesis	rapidly progressive severe tetraparesis	moderate tetraparesis	slight tetraparesis	moderate tetraparesis
GBS disability scale at onset (0-6)	4	4	4	3	2
motor symptoms at last follow-up	slight paraparesis	none	severe tetraparesis wheel-chair-bound	slight tetraparesis	moderate tetraparesis distal = proximal legs > arms
GBS disability scale at last follow-up (0-6)	2	0	4	3	2
sensory symptoms	pallhypesthesia	pallhypesthesia	distal dysesthesia, paresthesia, hypesthesia, pallhypesthesia	distal paresthesia, hypesthesia, pallhypesthesia, analgesia of feet, thermoanesthesia	distal paresthesia, pallhypesthesia, hypalgesia

autonomic symptoms	none	tachycardia, loss of heart rate variability	urinary retention chronic obstipation	orthostatic dysregulation	none
sensory ataxia	not present	present	not present	present	present
neuropathic pain	not present	cervicobrachialgia	present	present	present
anti-neuropathic analgesic treatment	none	none	pregabalin 600mg/d	gabapentin 600mg/d Tramadol 300mg/d	Tilidin/Naloxon when needed
tremor	not present	not present	not present	not present	action tremor in course of disease
respiratory insufficiency	not present	not present	not present	not present	not present
days of intensive care treatment	6	20	4	none	none
cranial nerve involvement	not present	unilateral peripheral facial palsy	not present	bilateral peripheral facial palsy	not present
further features	none	none	renal insufficiency in course of disease	none	none
reflexes	areflexia	areflexia	areflexia	areflexia	areflexia
GQ1b, GD1b, GM1 antibodies	negative	negative	negative	negative	negative
total IgG serum (g/l)	9.66	12.3	8.49	11.8	11.1
total IgM serum (g/l)	1.19	1.49	0.58	2.3	1.6
CSF analysis - *cell count/µl* - *protein (mg/l)* - *oligoclonal bands* - *CSF IgG index* - *antibody specificity index (ASI)*	 0/µl 752 no 0.54 -	 3/µl 705 no 0.55 -	 1/µl 842 no 0.46 0.08	 4/µl 1270 no 0.59 -	 3/µl 4084 no 0.62 0.89
quantitative sensory testament	n.d.	n.d.	no small fiber pathology	n.d.	n.d.
nerve conduction studies (NCS) at peak	<u>motor</u>: DML ↔ 4/4 nerves NCV ↔ 4/4 nerves loss of F-waves in 1/2 nerves CMAP ↓ 4/4 nerves conduction block in median nerve	<u>motor</u>: DML↑ 3/7 nerves NCV ↔ 7/7 nerves F-wave latency↑/ loss of F-waves in 5/5 nerves CMAP ↓ 1/7 nerves	<u>motor:</u> DML ↑ 2/4 nerves NCV ↓ 1/4 nerves F-wave latency↑ / loss of F-waves in 4/4 nerves conduction block in tibial nerve	<u>motor:</u> DML ↑1/4 nerves NCV ↓ in 2/3 nerves F-wave latency ↑ / loss of F-waves in 3/3 nerves CMAP ↓ 2/3 nerves conduction block in peroneus nerve	<u>motor:</u> DML↑ in 4/4 nerves NCV ↓ 4/4 nerves loss of F-waves in 3/3 nerves CMAP ↓ 2/4 nerves

nerve conduction studies (NCS) at peak	sensory: NCV ↔ 2/3 nerves SNAP ↓ 1/3 nerves loss of SNAP in 1/3 nerves	sensory: NCV ↓ in 1/4 nerves SNAP ↓ in 1/4 nerves	sensory: NCV ↓ in 1/3 nerves SNAP ↓ in 1/3 nerves loss of SNAP in 2/3 nerves	sensory: NLG ↓ 1/2 nerves SNAP ↓ 1/3 nerves	sensory: NCV ↓ 1/2 nerves SNAP ↓ 1/2 nerves
electromyography	spontaneous activity pseudo-myotonic discharge	n.d.	n.d.	no spontaneous activity	denervation spontaneous activity
sural nerve biopsy	n.d.	n.d.	n.d.	n.d.	axonal loss no signs of demyelination
pathological MRI result	n.d.	cervical lymphadeno-pathy	cervical herniated discs (C5/6, C6/7) with absolute (C6/7) and relative (C5/6) spinal stenosis	lumbar herniated discs (L4/5) with dorsal root compression	cervical herniated discs (C3/4) with relative spinal stenosis cauda equina gadolinium enhancement
response to treatment at onset					
- *IVIg*	n.d.	150g no motor improvement	200g no motor improvement	150g rapid improvement	200g slight improvement
- *plasma exchange*	rapid improvement after 6 PE	rapid improvement	n.d.	n.d.	n.d.
- *corticosteroids*	n.d.	n.d.	n.d.	n.d.	n.d.
response to treatment in course of disease					
IVIg	n.d.	n.d.	n.d.	26 cycles of IVIg (70g/cycle) loss of therapeutic effect in course of disease	25 cycles of IVIg (100g/cycle) with improvement, paused in 2017
plasma exchange	n.d.	n.d.	n.d.	n.d.	n.d.
corticosteroids	n.d.	n.d.	n.d.	n.d.	n.d.
further treatment	n.d.	n.d.	n.d.	n.d.	n.d.

Abbreviations: ↑ = increased, ↓ = decreased, ↔ = normal, CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, CMAP = compound motor action potential, CSF = cerebrospinal fluid, d = day, DML = distal motor latency, GBS = Guillain-Barré-syndrome, IVIg = intravenous immunoglobulins, MRI = Magnetic Resonance Imaging, n.a. = not applicable, n.d. = not done, n.d.a. = no data available, NCV = nerve conduction velocity, NCS = nerve conduction studies, OD = optical density, PE = plasma exchange, SNAP = sensory nerve action potential.

Patient 1 was a 61-year-old woman who was admitted to the intermediate care unit (IMC) because of severe and rapidly progressive proximal symmetric sensorimotor flaccid tetraparesis with only slight sensory impairment. Acute motor-sensory axonal neuropathy (AMSAN) was diagnosed, since clinical course and CSF results were typical of GBS, but nerve conduction studies showed reduced amplitudes without signs of demyelination. Pseudomyotonic discharges were detected via electromyography in two affected muscles. Plasma exchange led to rapid improvement of paresis. The patient was released to rehabilitation only 16 days after admission with only very light residual deficits. No follow-up visit was documented on the neurologic ward after monophasic course of GBS.

Patient 2, a 59-year-old woman, was admitted to the hospital because of distal and proximal, asymmetric, rapidly progressive, severe tetraparesis. The patient showed unilateral facial paresis. Multimodal sensory impairment with sensory ataxia as well as neuropathic pain was present. Due to autonomic symptoms (tachycardia) and severe motor involvement, treatment on the intensive care unit (ICU) was necessary for 20 days. CSF analysis showed moderately elevated protein levels at normal cell count. Electroneurography did not reveal reduction of nerve conduction velocities, but reduced F-waves and prolonged distal motor latencies as signs of proximal involvement in multiple motor nerves. The patient did not improve after therapy with IVIg, but there was quick recovery after plasma exchange and the patient was released to rehabilitation. Full strength was recovered within a year after onset and treatment.

Patient 3 was a 74-year-old woman initially diagnosed with GBS because of rapidly progressive distal and proximal tetraparesis and sensory deficits, cytoalbuminologic dissociation in CSF analysis and electrophysiological features concordant with the Brighton criteria (1). There was no cranial nerve or autonomic involvement, nor further symptoms such as tremor or ataxia. Nerve conduction studies of motor nerves revealed conduction block in one nerve and prolonged/ lost F-waves, whereas nerve conduction velocity was only reduced in 1 out of 4 nerves. Treatment on the intensive care unit (ICU) was necessary due to severity of symptoms. Therapy with IVIg did not lead to motor improvement. With symptoms not improving within 28 days, the patient was diagnosed as CIDP. At discharge to rehabilitation clinic, she had to use a wheel-chair bound. There was no further improvement of symptoms during 6 weeks of rehabilitation. Severe neuropathic pain occurred during the course of disease and had to be treated with oxycodone 10mg/d and pregabaline 600mg/d. Sensory impairment worsened during rehabilitation. The patient developed renal insufficiency of unknown cause. She needed permanent catheter due to urinary retention and developed chronic obstipation. Diagnostic reevaluation at a neurologic ward was recommended when discharged to short-term-care, but unfortunately, the patient was lost to follow-up.

In patient 4, a 68-year-old woman, GBS was diagnosed at admission to the university hospital of Kiel in 2001, as she had developed rapidly progressive, distal and proximal moderate sensorimotor flaccid tetraparesis with bilateral facial palsy, multimodal sensory involvement and neuropathic pain. Cytoalbuminologic dissociation was

present in CSF. Due to initially normal nerve conduction studies, diagnostic certainty according to the Brighton criteria was at level 4. Treatment with 150g of IVIg led to rapid improvement of symptoms. She did not need further treatment and showed remission of motor symptoms. After a recovery phase of several months and a long oligosymptomatic period with residual hypesthesia and paresthesia of the legs (exact duration unknown because of retrospective assessment of data and intermediate loss to follow-up), the patient developed relapse remitting sensory CIDP with neuropathic pain, which lead to hospitalization in 2011. MRI scan revealed lumbar herniated discs with dorsal root compression as possible competing cause of neuropathic pain, but symptoms also affected upper extremities. Nerve conduction studies showed demyelinating features at sensory and motor nerves. Treatment with IVIg was initiated. Improvement of motor symptoms and nerve conduction studies of motor nerves was documented, but sensory symptoms and sensory nerve conduction studies (NCV and CMAP) worsened. Furthermore, the patient reported progressive gait instability and neuropathic pain. In 2014, IVIg was stopped due to a loss of the therapeutic effect. At that timepoint, IgG subclass had already switched to IgG4 (serum sample from 2011). The assessment had been done retrospectively and therefore had not been considered in diagnostic and therapeutic workup. The patient did not receive further immune-modulatory treatment in our hospital and was lost to clinical follow-up in 2015.

Patient 5, a 47-year-old man, developed slight to moderate distal sensorimotor flaccid tetraparesis with sensory ataxia with peak of symptoms at 90 days. There was no cranial nerve or autonomic involvement, nor neuropathic pain. CSF analysis showed highly elevated protein levels. ENG revealed both distal and proximal demyelinating as well as axonal features, with sural sparing in sensory nerves and signs of denervation in electromyography. Cranial MRI showed cauda equina gadolinium enhancement as sign of radiculitis. Treatment with IVIg led to improvement of symptoms. The patient could therefore be discharged home. Six weeks after first assessment, patient 2 was hospitalized again due to severe sensorimotor tetraparesis with neuropathic pain which led to immobility and wheel-chair-dependency. CSF still showed highly elevated protein levels. Sural nerve biopsy (six months after onset of the symptoms) showed moderate axonal loss with minor perivascular inflammation, but without signs of de- or remyelination. Sural nerve teased fibers for the study of paranodal pathology were not available. The patient was diagnosed CIDP and therapy with corticosteroids and IVIg was initiated. After first improvement of symptoms, regular IVIg cycles were initiated and led to slow, but continuous sensorimotor improvement with reduction of neuropathic pain. IVIg was stopped after 25th cycle. At that time point, the patient presented with slight sensorimotor impairment with distal, asymmetric moderate paresis and sensory ataxia. Symptoms remained stable for more than 12 months without further treatment. Serologic studies revealed reduction of IgG-titer of anti-Caspr-1 corresponding to clinical amelioration.

References : 1) Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barre syndrome and validation of Brighton criteria. Brain 2014;137:33-43.