Area postrema syndrome as frequent feature of Bickerstaff brainstem encephalitis

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Abstract
Objective: Area postrema (AP) syndrome (defined as: nausea and/or emesis and/or singultus at onset of brainstem dysfunction) comprises complex pathophysiologic mechanisms triggered by different entities. The first objective was to assess the frequency of AP syndrome as a clinical feature in brainstem encephalitis (BE). Finding an especially high prevalence of AP syndrome in Bickerstaff brainstem encephalitis (BBE), we also analyzed the frequency of AP syndrome in other autoimmune diseases with anti-ganglioside antibodies (Guillain–Barré syndrome (GBS) and its variants).

Methods: We systematically evaluated the prevalence of AP syndrome in BE in all patients treated at our university hospital during a 15-year period. In a second step, BBE patients were compared to GBS and Miller Fisher syndrome (MFS) patients as clinical subtypes of a disease continuum without brainstem dysfunction. Results: We found AP syndrome in 8 of 21 BE patients, including 3 of 7 BBE and in 4 of 112 GBS/MFS patients. AP syndrome was as a frequent but under-recognized feature of BE with a significant impact on patients’ well being.

Interpretation: Manifestation of AP syndrome in BBE but also in GBS and its subtypes point toward a role of autoimmune antibodies that should be investigated in future studies. Considerable misdiagnosis or nonrecognition complicates diagnostic and therapeutic management. Therefore, AP syndrome should be considered in any episode of otherwise unexplained nausea, emesis, or singultus.

Introduction
Area postrema (AP) syndrome is characterized by intractable nausea, emesis, and singultus¹ caused by various mechanisms involving the AP and nearby brainstem structures harboring the chemoreceptor trigger zone (CTZ) of the „vomiting center“ that receives input from the abdominal vagus,² vestibular region, higher cortical and thalamic centers, and chemoreceptors of the AP.³ Belonging to the sensory circumventricular organs,⁴ the AP fulfills an exclusive function in chemotactic sensing between the central nervous system (CNS) and the blood stream with the blood–brain barrier (BBB) being replaced by specialized capillaries ⁴,⁵ permeable to certain substances.⁶ The chemoreceptors of AP neurons are easily accessible for endo- and exogenous substances and multiple neurotransmitters are involved in the emetic reflex.⁷ However, some trigger pathologies of AP syndrome are under-recognized since the exact pathophysiologic mechanisms are not fully understood. Basically, AP lesions and longitudinally extensive myelopathies of diverse etiologies can trigger AP syndrome. Most often, they are attributable to inflammatory entities. Also, neoplastic brainstem lesions can present with AP syndrome.⁸–¹¹ In addition, AP syndrome can be caused by irritation of the CTZ at the molecular level which does not necessarily show up in lesions detected by magnetic resonance imaging (MRI) as known from drug-induced AP syndrome.³ There is evidence about an association between AP syndrome and antibody-mediated disorders like neuromyelitis optica and neuromyelitis optica spectrum

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disorders (NMO/NMOSD), often presenting longitudinal brainstem lesions and AP syndrome was recognized as a core characteristic by the International Panel for NMO Diagnosis. AP lesions in multiple sclerosis (MS) seem to provoke AP syndrome less frequently than comparable NMO lesions. This suggests additional trigger mechanisms beyond the mere localization of lesions and has led to the hypothesis that there is a causative role played by antibodies in AP syndrome. Supporting this hypothesis, AP syndrome was described in paraneoplastic brainstem encephalitis (BE). Pathogenic autoimmune antibodies (anti-ganglioside antibodies) likewise play a role in Bickerstaff brainstem encephalitis (BBE), the CNS subtype of Miller Fisher syndrome (MFS). Atypical manifestations and an overlap with different variants of Guillain–Barré syndrome (GBS) are reported, altogether representing a clinicopathological continuum with variable involvement of the peripheral (PNS) and the central nervous system (CNS). There is a report of a GBS patient with intractable nausea and emesis interpreted as having cyclic vomiting syndrome, a chronic condition with recurrent emesis of unknown cause requiring exclusion of CNS disease. Remarkably, the report conveys uncertainty regarding the diagnosis of GBS in view of numerous symptoms reported, suggesting CNS involvement and a potential AP syndrome explaining emesis in the particular patient. Further, single reports comment on otherwise unexplained emesis in infectious BE without explicitly placing these symptoms in the context of a quite conceivable AP syndrome.

We retrospectively evaluated the prevalence of AP syndrome in all consecutive cases of BE of different pathologies, including BBE treated at our department over a 15-year period. In a second step, we assessed the frequency of AP syndrome in GBS and its variants in comparison to BBE.

**Figure 1.** Study design. Our retrospective study approach to systematically evaluate the prevalence of AP syndrome in BE, including BBE in all consecutive patients treated at our university hospital during a 15-year period is depicted. BBE was compared to GBS and MFS.
Patients and Methods

Study design and population

To assess the frequency of AP syndrome in BE, we first performed a systematic retrospective observational study of all BE patients \((n = 21)\) treated at the Department of Neurology, University Hospital, Goethe University, Frankfurt am Main. Patients were identified through a database search of our hospital information system (ORBIS software, Agfa HealthCare, Bonn, Germany) for patients with a discharge diagnosis of DRG G04.8 (including encephalitis, myelitis, and encephalomyelitis, not specified) between January 2002 and September 2017 followed by a review of each patient record for the BE criterion. Patients with a discharge diagnosis G04.8 not showing evidence of BE in the patient record \((n = 118)\) were excluded (Table S1).

Finally, 21 BE patients were included in the analysis: \(N = 7\) BBE patients (including GBS/BBE overlap), \(n = 9\) patients with autoimmune BE of unknown cause (including \(n = 2\) BE patients potentially related to systemic lupus erythematosus (SLE)), \(n = 1\) patient with Morvan’s syndrome, \(n = 1\) patient with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), \(n = 3\) patients with infectious BE (tuberculosis (TB), listeria monocytogenes, bacterial clival osteomyelitis).

With BBE representing the CNS subtype of MFS, we next investigated BBE patients in comparison to MFS \((n = 7)\), GBS/MFS overlap \((n = 7)\) and GBS \((n = 98)\) patients, likewise treated at the Department of Neurology, University Hospital, Goethe University, Frankfurt am Main, Germany between January 2002 and September 2017 (Fig. 1).

Patients were identified by a database search of our hospital information system (ORBIS software, Agfa HealthCare, Bonn, Germany) for patients with a discharge diagnosis of DRG G61.0 (including GBS and MFS) between January 2002 and September 2017 followed by a review of each patient record. For diagnosis of GBS, MFS, their subtypes and overlapping conditions, we applied clinical diagnostic criteria as proposed by the GBS classification group\(^2^2\) and exclusion of differential diagnoses. Clinical criteria for BBE, the CNS subtype of MFS, were ophthalmoplegia, ataxia, and hypersomnolence. Antiganglioside antibody (asialoganglioside GM1, gangliosides GM1, GM2, GD1a, GD1b, GQ1b) testing was performed in several

| Nr. | Sex | Age | Entity                          | Nausea/emesis/singultus | Original symptom evaluation | Autoimmune antibodies | MRI | Tx       | O (month) |
|-----|-----|-----|---------------------------------|--------------------------|-----------------------------|------------------------|-----|----------|-----------|
| 1   | m   | 33  | autoimmune                     | y/n/y                   | NA                          | NA                     | y   | IVMP     | CR (2)    |
| 2   | m   | 54  | autoimmune                     | y/y/n                   | NA                          | 1\(^{st}\)GQ1b neg.   | y   | IVMP     | CR (4)    |
| 3   | f   | 51  | autoimmune, possible SLE       | y/y/n                   | NA                          | 1\(^{st}\)dsDNA, ANA, APL pos., GQ1b neg. | y   | OP, AZA, IVMP | IR (4)    |
| 4   | m   | 54  | BBE/GBS                        | y/y/y                   | GE                          | 2\(^{nd}\)GQ1b neg.   | y   | IVMP     | CR (7)    |
| 5   | m   | 63  | BBE                            | y/y/n                   | GE                          | 2\(^{nd}\)GM1, GM2, GD1a, GD1b, GQ1b neg. | y   | IVMP     | CR (1)    |
| 6   | m   | 66  | BBE                            | y/y/y                   | correct                     | 1\(^{st}\)GM1 (118%), GM2 (45%), GD1a (115%), GD1b (175%), Asialo-GM1 (45%), GQ1b neg. | n   | IVMP, 9xPP, 12xPP | IR (2)\(^a\) |
| 7   | f   | 58  | bacterial clival osteomyelitis  | y/y/n                   | correct                     | NA                      | y   | AB       | IR (5)\(^b\) |
| 8   | m   | 42  | TB                             | y/y/n                   | vestibulo pathy             | NA                      | y   | AB       | IR (3)    |

Clinical data of patients with BE and manifestation of AP syndrome are depicted.
AB, antibiotics; AP, area postrema; AZA, azathioprine; BBE, Bickerstaff brainstem encephalitis; BE, brainstem encephalitis; CR, complete remission; f, female; GE, gastroenteritis; IR, incomplete remission; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; m, male; MRI, Magnetic resonance imaging; n, no; NA, not available; neg., negative; OP, oral prednisone; pos, positive; PP, plasmapheresis; SLE, Systemic lupus erythematosus; TB, tuberculosis; Tx, treatment; y, yes.

MRI: MRI brainstem lesions.

Autoimmune antibodies: Timing of antibody testing \(^{1}\) = pretreatment, \(^{2}\) = posttreatment, \(^{NA}\) = not available.

\(^{a}\)IR until death of sepsis after 2 months of follow-up.

\(^{b}\)IR in 01/2018 after 5 months of follow-up, further improvement expected under AB therapy.
patients, though it was not mandatory for diagnosis of GBS, MFS and its variants according to the diagnostic criteria. Timing of antibody testing in relation to treatment was indicated. In a BBE patient with AP syndrome (patient 6), we additionally investigated the evolution of anti-ganglioside antibody titers before and after treatment.

Demographic and clinical data (pathogenic antibodies, MRI brainstem lesions, treatment) were extracted from patients’ records, deidentified, and entered into password-protected databases. All patients received a thorough differential diagnosis clarification (laboratory screening including serum analysis for HIV, syphilis, borreliosis, rheumatism, and sarcoidosis). Patients’ records and MRI images were screened by a board-certified neuroradiologist (MME) for suggestive clinical and MRI characteristics to rule out NMO/NMOSD according to the international consensus diagnostic criteria.

Variables for diagnosis of AP syndrome

Variables to assess incomplete (1–2 symptoms) or complete AP syndrome were otherwise unexplained, intractable nausea, emesis, and singultus mentioned in patient records at or after onset of neurological symptoms, without additional non-CNS symptoms. Since confusion of AP syndrome with gastrointestinal disorders was a potential bias, we screened patient records for suggestive clinical or laboratory signs and verified that intractable nausea and emesis occurred concomitantly with and not prior to the onset of neurological features to rule out an infection. In patients meeting our criteria for AP syndrome without being described as such, we included the original symptom evaluation.

Follow-up and statistical analysis

Follow-up data regarding remission of neurological deficits and AP syndrome were extracted retrospectively from follow-up appointments documented in patient records in an observation period up to January 2018. Missing or incomplete follow-up data was indicated. Descriptive statistics (median, 25-to-75% interquartile range (IQR) and percentages) were used to summarize demographics.

Results

AP syndrome in brainstem encephalitis

In total, 8 of 21 (38.1%) BE patients (median age 51, IQR 36–62 years) showed incomplete (n = 6, 28.6%) or complete (n = 2, 9.5%) AP syndrome (Tables 1 and 2). AP syndrome was also observed in BE patients (patients 3 and 6) without MRI brainstem lesions (Table 1). Images of two representative patients (patients 2 and 4) with typical MRI brainstem lesions in the context of BE were
depicted (Fig. 2). Follow-up data showed complete remission (CR) in most patients (Table 1). Patient 6 achieved marked yet incomplete remission (IR) up to death from sepsis after 2 months of observation. Patient 7 presented IR after 5 months of follow-up, although further improvement could be expected under antibiotic therapy.

**AP syndrome in GBS and its subtypes**

In this study, 3 of 7 (42.9%) BBE patients (median age 63, IQR 59–65 years) demonstrated AP syndrome (Table 1). Additionally, 4/112 (3.6%) patients with GBS variants without brainstem dysfunction (Tables 3 and 4) showed AP syndrome ($n = 98$ GBS (median age 52, IQR 36–62 years), $n = 7$ MFS (median age 53, IQR 31.5–75.5 years), $n = 7$ GBS/MFS overlap (median age 54, IQR 45.5–67.5 years) patients)). Although there was no clinical, radiological and/or electrophysiological brainstem involvement in these patients and supportive diagnostics (CSF, nerve conduction studies) pointed toward GBS or GBS/MFS, mild CNS involvement within the clinical continuum of GBS variants could not be fully excluded. Patient 24 presented nearly CR at discharge after 1 week of observation with no further follow-up data available; therefore, CR is conceivable. Patient 25 showed IR after 3 months of follow-up and further improvement was expected.

**Underrecognition and misdiagnosis of AP syndrome**

AP syndrome was indicated in the medical records of only 2/12 (16.7%) patients, but unrecognized ($n = 4$, 33.3%) or misdiagnosed ($n = 6$, 50%) in the majority of patients.
patients. Most frequently \((n = 5, 41.7\%)\), symptoms were attributed to gastroenteritis (Tables 1 and 3) even though there were no supportive signs indicating an infection and symptom onset was concomitant with and not prior to the onset of the other neurological deficits making AP syndrome more probable.

**Outcome**

AP syndrome, usually occurring simultaneously with the other neurological symptoms, generally responded well to causal and symptomatic treatment with most patients showing CR. In patient 6 (Tables 1 and 5), we established an anitiemetic treatment regime comprising the 5-HT3-receptor antagonist granisetron, the Neurokinin-1 receptor (NK1R) antagonist aprepitant, dexamethasone, and haloperidol. Combined with combinational causal treatment with IVMP (1 g/day for 5 days), IVIGs \((3 \times 10 \ g/day \ for \ 5 \ days)\) and 12 cycles of plasmapheresis, we observed marked improvement of general well-being and the neurological condition including AP syndrome correlating with a decrease of anti-ganglioside antibodies (Table 5). Because of the significant impact of AP syndrome on patients’ moods, concomitant antidepressant treatment (duloxetine) was necessary. Despite marked improvement of neurological deficits and AP syndrome in a follow-up period of 2 months, patient 6 died unexpectedly of fulminant sepsis acquired during the postdischarge period.

**Discussion**

AP syndrome\(^1\) originates from complex pathophysiologic mechanisms triggered by several different pathologies. Besides structural AP lesions, there is growing evidence that pathogenic antibodies in AQP-4 IgG–seropositive NMO/NMOSD\(^{12-15}\) or GABA-B-receptor antibodies in paraneoplastic BE\(^{21}\) might trigger AP syndrome. This hypothesis might be supported by the findings of this retrospective study. We showed that AP syndrome is a frequent but often mis- or undiagnosed clinical feature of BE. Manifestation of AP syndrome did not require MRI brainstem lesions in our cohort, being in line with drug-related AP syndrome\(^3,28,29\) or a study investigating 62

### Table 3. Characteristics of Guillain-Barré syndrome patients with AP syndrome.

| Nr. | Sex | Age | GBS variant | Nausea/ emesis/singultus | Original symptom evaluation | Autoimmune antibodies | MRI | Tx | O (month) |
|-----|-----|-----|-------------|--------------------------|---------------------------|-----------------------|-----|----|----------|
| 22  | f   | 38  | GBS/MFS     | y/y/h                    | GE                        | NA                    | NA  | IVIG | CR (12)  |
| 23  | f   | 54  | GBS/MFS     | y/y/h                    | GE                        | 2GM1 (36%), GM2 (42%), GD1a, GD1b, GQ1b neg. | n   | IVIG | IR      |
| 24  | m   | 21  | GBS         | y/y/h                    | GE                        | NA                    | NA  | IVIG | NA\(^*\) |
| 25  | f   | 56  | GBS         | y/y/h                    | NA                        | 2GM1, GM2, GD1a, GD1b, GQ1b, Asiaolo-GM1 neg. | n   | IVIG | IR (3)\(^b\) |

Clinical data of GBS and GBS/MFS patients with manifestation of AP syndrome are depicted. AP, area postrema; CR, complete remission; f, female; GBS, Guillain–Barré syndrome; IR, incomplete remission; IVIG, intravenous immunoglobulin; m, male; MRI, Magnetic resonance imaging; n, no; NA, not available; O, outcome; PP, plasmapheresis; Tx, treatment; y, yes.

MRI: MRI brainstem lesions.

Autoimmune antibodies: Timing of antibody testing \(^1\) = pre-treatment, \(^2\) = posttreatment, \(^NA\) = not available.

\(^a\)IR after 1 week of follow-up, no further follow-up data available, CR expected.

\(^b\)IR in 01/2018 after 3 months of follow-up, further improvement expected.

### Table 4. Frequency of AP syndrome in subtypes of Guillain–Barré syndrome.

| Variable | Total \((n = 119)\) | BBE \((n = 7)\) | MFS \((n = 7)\) | GBS/MFS \((n = 7)\) | GBS \((n = 98)\) |
|----------|---------------------|----------------|----------------|---------------------|----------------|
|          | n (%) or median     | n (%) or median | n (%) or median | n (%) or median     | n (%) or median |
| Male sex | 84 (70.6)           | 5 (71.4)       | 5 (71.4)       | 5 (71.4)            | 69 (70.4)      |
| Age, y   | 53 (37.75–63.25)    | 63 (59–65)     | 53 (31.5–75.5) | 54 (45.5–67.5)      | 52 (36–62)     |
| AP syndrome | 7 (5.9)             | 3 (42.9)       | 0 (0)          | 2 (28.6)            | 2 (2)          |

Demographic data and frequency of AP syndrome in the total patient cohort and in the subcohorts of BBE, MFS, GBS/MFS overlap and GBS patients are depicted. AP, area postrema; BBE, Bickerstaff brainstem encephalitis; GBS, Guillain–Barré syndrome; MFS, Miller Fisher syndrome; GBS/MFS, GBS/MFS overlap; y, years.
symptomatic BBE patients that showed MRI abnormalities in only 30% of the cases and even less in BBE patients with overlapping GBS.30 A brain autopsy of a BBE patient without evident MRI brainstem lesions did however reveal perivascular lymphocytic infiltration and edema,30 which might also apply to patients of our cohort without suggestive MRI abnormalities. Interestingly, we observed AP syndrome in individual patients with GBS and GBS/MFS (Tables 3 and 4) as clinical subtypes without brainstem dysfunction in contrast to BBE, the latter representing the CNS subtype of MFS. Of these, in only 4 out of the total of 112 patients with GBS, GBS/MFS overlap and MFS (Tables 3 and 4), did AP syndrome occur simultaneously to the onset of the other neurological symptoms and generally responded well to causal treatment with IVIG. Besides the much lower prevalence of AP syndrome in contrast to BBE (Table 1), we further observed a milder manifestation without the development of a complete AP syndrome, including intractable nausea, emesis, and singultus1 in the affected patients with GBS and GBS/MFS. Given the clinicopathological continuum of GBS, MFS and its variants, including BBE,24 mild CNS involvement in the aforementioned patients can not be fully excluded, although, there was no supportive clinical, electrophysiologic, or radiographic evidence for brainstem involvement. The clinical variations of distinct GBS and MFS subtypes might be related to the locoregional distribution of different ganglioside species22,31 in glial and neuronal membranes of PNS and CNS accessible to circulating anti-ganglioside antibodies that provoke a complex inflammatory response.32 Although topospecific mapping of brain gangliosides is challenging, as demonstrated in animal models, a spatial distribution could be detected demonstrating a predominant expression of certain ganglioside species in the brainstem and periaqueductal grey area (GD1, GT1, GT3, GQ1).33 Due to technical limitations, there are only a few single patient or small cohort studies on human fetal CNS focusing on predefined regions like the hippocampus24,33 or the cerebellum.36 The detection of ganglioside species in close proximity to the AP33 together with limited experimental and histopathologic data12,14 and our clinical observations indicate a potential role of pathogenic anti-ganglioside antibodies in AP syndrome. Clearly, these findings should be confirmed in larger cohorts of prospective future studies, since the retrospective approach was a limitation in terms of the accuracy of clinical evaluation. The exploration of the functional mechanisms of a potential impact of autoimmune antibodies on the AP’s CTZ should be a focus for future studies. However, antibody testing (especially for anti-AQP-4-IgG but also anti-ganglioside antibodies) appears useful in patients with AP syndrome to detect underlying autoimmune disorders that would warrant respective treatment. It could especially be useful for patients without evident MRI brainstem lesions or additional sings of brainstem dysfunction. Since antibody titers can be inconclusive, depending on the timing of the analysis in relation to therapy initiation (Table 5) and some BBE patients are even seronegative for canonical anti-GQ1b antibodies,30 we recommend a broad screening for anti-ganglioside antibodies (Table 5) expressed in different GBS subtypes24 prior to the initiation of causal therapies. Although not mandatory for diagnosis of GBS and its variants,22 the inconsistency of extent and timing of antibody testing was a limitation in our retrospective study and might also explain the relatively high rate of BBE patients without detection of anti-GQ1b antibodies in our cohort. Semiologic overlap of AP syndrome with non-CNS disorders leads to nonrecognition and misdiagnosis. The severe impact on patients’ wellbeing (aspiration, malnutrition, electrolyte disorders, serious mood disorders) caused by AP syndrome should be a reason for identifying trigger diseases, particularly because AP syndrome is an easily treatable syndrome if identified correctly. AP syndrome should be considered in any episode of otherwise unexplained and intractable nausea, emesis or singultus, especially in combination with neurological deficits indicating brainstem dysfunction. We recommend contrast-enhanced brain MRI, CSF analysis, neurophysiological examination in addition to anti-ganglioside and anti-AQP-4-IgG antibody testing, the latter to rule out NMO/NMOSD as a common trigger for AP syndrome.12-15 Besides causal treatment, a multimodal anti-emetic concept is crucial for the management of AP syndrome. Due to its manifold triggers and complex pathophysiology, there are no specific studies or treatment guidelines. However, there is some evidence from drug-induced AP syndrome.3 We emphasize the importance of a multimodal combinational therapy targeting the CTZ: besides 5-HT3-receptor antagonists with major effects on

| Table 5. Anti-ganglioside antibody titers in a patient with Bickerstaff brainstem encephalitis and AP syndrome. |
|-----------------------------------------------|
| Anti-ganglioside antibody | Pretreatment-titer (%) | Posttreatment titer (%) |
|---------------------------|------------------------|------------------------|
| Asialoganglioside GM1     | 45                     | <30                    |
| Ganglioside GM1           | 118                    | 33                     |
| Ganglioside GM2           | 45                     | <30                    |
| Ganglioside GD1a          | 115                    | 36                     |
| Ganglioside GD1b          | 157                    | 41                     |
| Ganglioside GQ1b          | <30                    | <30                    |

Evolution of serum anti-ganglioside antibody titers in patient 6 before and after treatment with 5 × 1 g intravenous methylprednisolone, 5 × 30 g IVIG and 12 cycles of plasmapheresis (reference: <30% = negative, 30-50% = borderline, 51–100% = positive, 100-% = highly positive).
peripheral vagal afferents, NK1R-receptor antagonists are effective and well-established antiemetic agents acting in the brainstem. Δ9-tetrahydrocannabinol is likewise reported to target emetic brainstem centers. Furthermore, a case study reports the effects of low-dose amitriptyline in GBS with conceivable AP syndrome.25 Our findings suggest that neurologists should be aware of the occurrence of AP syndrome as a relevant but yet under-recognized clinical characteristic of BE at a percentage level of 38.1% in our cohort, demonstrating a significant impact on patients’ wellbeing. From our observations in BBE, MFS, and GBS patients, a pathophysiologic role of autoimmune antibodies is conceivable and should be investigated in further studies.

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Author Contributions

Concept and design of study: PSZ and WP. Acquisition and analysis of data: PSZ, AB, MME, HS, and WP. Drafting of the manuscript: PSZ and WP.

Conflicts of Interest

No conflict of interest regarding the publication of this article.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Excluded patients. Differential diagnosis of patients identified by our database research, but excluded after review of patients’ records was depicted. None of the patients showed BE.