Short Communication

Epidemiology of neuronal surface antibody-mediated autoimmune encephalitis and antibody-based diagnostics

Luigi Zuliani [a,b,*], Sabrina Marangoni [c], Piera De Gaspari [b], Irene Rosellini [d], Margherita Nosadini [e,b], Joanne M. Fleming [f], Valentina De Riva [a], Elisabetta Galloni [a], Francesco Perini [a], Anna Chiara Frigo [g], Stefano Sartori [e,b], Marco Zoccarato [f,b], Bruno Giometto [c]

[a] Department of Neurology, Ospedale San Bortolo, Azienda ULSS8 Berica, Via Rodolfi 37, 36100 Vicenza, Italy
[b] Neuroimmunology Group, Pediatric Research Institute "Città della Speranza", Padova, Italy
[c] Department of Neurology, Ospedale Santa Chiara, Trento, Italy
[d] Department of Neurology, Azienda ULSS2 Marca Trevigiana, Treviso, Italy
[e] Department of Women's and Children's Health, Pediatric Neurology and Neurophysiology Unit, Azienda Ospedaliera-University of Padua Medical School, Italy
[f] Department of Neurology, O.S.A., Azienda Ospedaliera-University of Padua Medical School, Italy
[g] Department of Cardiac, Thoracic, and Vascular Sciences, Azienda Ospedaliera-University of Padua Medical School, Italy

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ABSTRACT

Epidemiologic data on neuronal surface antibody (NSAb)-associated autoimmune encephalitides (NSAE) are scarce and heterogeneous. We review our 13-year-long biobank-data collection and provide the incidence of NSAE in two Italian provinces (approx. Population of 1,400,000) over a 5-year period (July 2013–June 2018). NSAbs were diagnosed in 75 out of 1179 tested patients (6.4%). The most common NSAbs were anti-LGI1 (30 cases), followed by NMDAR (24). Eleven cases of NSAE were diagnosed in Treviso and Trento provinces with an estimated incidence of 1.54 per 1,000,000 population (LGI1-encephalitis 0.84; C.I. 0.38–1.88). LGI1-E is the most frequent NSAE among adults.

1. Introduction

The incidence of autoimmune encephalitis (AE) is approximately 1–5 cases per million population (Granerod et al., 2010) (Dubey et al., 2018). However, adequate epidemiological studies on neuronal-surface antibody (NSAb)-associated AE (NSAE) (Dalmau and Graus, 2018) are lacking because NSAE have been characterized only recently, are probably underrecognized, and there is no defined diagnostic gold standard.

With the aim to determine the frequency of NSAb detection over the years, we retrospectively evaluated the 13-year-long biobank-data collection by our Neuroimmunology Service. From our pool of positive samples we analysed the NSAE cases followed at the reference hospitals of Trento and Treviso (north-east Italy) to provide incidence rates over a 5-year period.

2. Population and methods

2.1. Frequencies and trends in NSAb diagnostics

In 2005, collection of samples and patient data for NSAb testing started at the Neuroimmunology Service in Padova (Giometto et al., 1994) (Vianello et al., 2004). Initially, samples were sent to the reference laboratory in Oxford to be assayed for VGKC- and NMDAR-Abs (Irani et al., 2010a)(Irani et al., 2010b). Following commercialization of an indirect immunofluorescence cell-based assay (IIF-CBA), samples were tested at our own lab.

Between July 2013 and June 2018, a standard two-step diagnostic approach was applied (Zuliani et al., 2017): 1. IIF-CBA using fixed cell lines transfected with the antigen of interest (Euroimmun, Lübeck, Germany), according to the clinicians' request: a. Multiple biochip system ('mosaic') assay with the six most clinically relevant NSAb antigens (NMDAR, AMPAR1–2, GABAbR, LGI1, CASPR2); or b. NMDAR; or c. LGI1 and CASPR2; 2. Indirect immunohistochemistry (IIHC) on frozen

* Corresponding author.
E-mail address: luigi.zuliani@aulss8.veneto.it (L. Zuliani).

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rat brain tissue (tissue-based assay [TBA]) in the case of indeterminate results on IIF-CBA (Graus et al., 2016). A few selected cases were tested for GlyR-Abs at Oxford (Zuliani et al., 2014).

In order to compare the detection frequency of NSAbs with that of other available neural and glial antibodies at our Service, we reported data on GAD65-, Onconeural and Anti-aquaporin-4 antibodies (AQP4-Abs). GAD65-Abs were tested with a commercial ELISA kit (RSR Limited). Only concentration values above 2000 UI/mL were considered. Onconeural antibodies (Hu, Yo, Ma2, Ri, CV2/CRMP5, amphiphysin) were tested with a line-blot (Euroimmun) confirmed by TBA (Zoccarato et al., 2017). AQP4-Abs antibodies were tested with a commercial CBA (Euroimmun).

2.2. Epidemiologic analysis

We conducted a hospital-based study of the incidence of NSAb-positive AEs over a 5-year period in Treviso and Trento provinces. Between July 2013 and June 2018 all possible AE serum and CSF samples from the hospitals of Treviso and Trento provinces (both hub and spoke facilities) were referred to our Neuroimmunology Service. We included all NSAb-positive adult patients residing in Treviso and Trento provinces (global population of approx. 1,400,000) with a confirmed diagnosis of AE according to Graus' criteria (Graus et al., 2016), and prospectively followed them up.

3. Results

3.1. Neuronal surface antibody-positive patients

Between July 2013 and June 2018, 2898 samples (serum, CSF or both) from 1849 patients were tested and antibodies against neuroglial targets (NSAb, onconeural, GAD65, AQP4) were detected in 144 patients, with an overall percentage Ab-positivity of 7.79 (Table 1; Fig. 1).

NSAbs were diagnosed in 75 out of 1179 tested patients (6.36%), accounting for 52% of the total positive cases (75/144). The most common Abs were anti-LGI1 (30 cases), NMDAR (24) and CASPR2 (20). Other NSAbs included: AMPAR (2) and GABAbR (2). Dual positivity was detected in two patients: LGI1-CASPR2-Abs and CASPR2- GABAbR-Abs. One other case tested positive for GlyR-Abs.

Antineuronal antibodies with an intracellular target were identified in 51 patients: onconeural antibodies in 32; GAD65 (>2000UI/mL) in 20; one patient had dual positivity for onconeural and GAD65-Abs. Anti-AQP4 were found in 19 patients. One other case tested positive for Anti-AK5 antibodies at the reference lab in Barcelona (included in a previous study ([Zoccarato et al., 2019])).

3.2. Epidemiology of NSAE in Trento and Treviso provinces

During the 5-year study period, samples from 12 new adult patients hospitalized in Treviso and Trento provinces proved positive for NSAbs. Eleven had a final diagnosis of AE (5 females; age range 21–70) (see Table 2).

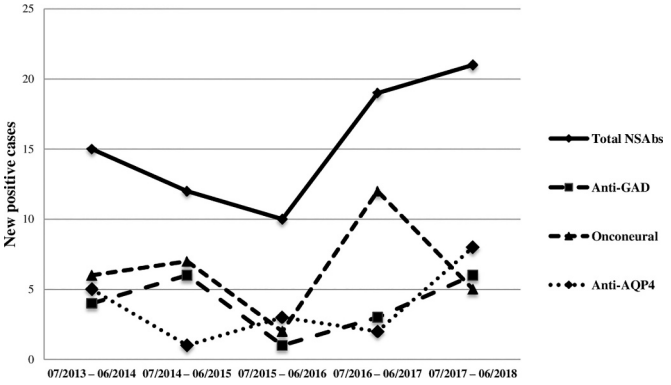

Fig. 1. Time course (trend) of new antibody diagnosis.

During the study period, Treviso and Trento provinces had a mean population of 886,153 (adult population [≥18-years] 712,382) and 537,117 (429,588 adults), respectively (Italian National Institute of Statistics [*dati.istat.it*]).

The incidence of NSAE in the total population of Trento and Treviso provinces was 1.54 per 1,000,000 persons per year (95% C.I. 0.86–2.79); in the adult population it stood at 1.93 per 1,000,000 persons per year (95% C.I. 1.07–3.48).

The incidence of LGI1- and NMDAR-encephalitis in the total population was respectively 0.84 (95% C.I. 0.38–1.88) and 0.42 (95% C.I. 0.14–1.31) per 1,000,000 persons per year; in the adult population it was 1.05 (95% C.I. 0.47–2.34) and 0.52 (95% 0.17–1.63).

Ten patients with NSAE diagnosed during the study period and five others diagnosed previously were alive at end of the study. The prevalence of NSAE was 10.5 and 13 per 1,000,000 inhabitants in the whole (1,427,318) and adult (1,150,372) population, respectively.

4. Discussion

The increasing number of NSAbs described in recent years and the presence of few centers with appropriate expertise suggest that these disorders could be underrecognized.

Our study adds evidence that NSAE are indeed rare, but increasingly recognized, and that LGI1-Ab is the most common neuronal antibody found in suspected AE, at least in adult patients.

Similarly to other research (McCracken et al., 2017)(Bien et al., 2020), the first aim of our study was to evaluate antibody findings over a 5-year period in which the diagnostic approach was homogenous (Zuliani et al., 2017) and without preliminary clinical selection.

Eight percent of cases were found positive for neuroglial targets (Table 1) and 6.4% for NSAbs. In the Philadelphia (US) study, a standard commercial CBA was combined with additional in-house live-CBA permitting to obtain 15.4% positivity for NSAb (McCracken et al., 2017). The rate of positivity in our investigation is comparable to a German

Table 1
Antibodies and frequencies – July 2013 – June 2018.

Antibodies	No. tested patients	No. positive	S +	CSF +	S/CSF +	% of positive	% of total ab-positive patients
Anti-NMDAR	1059	24	3	5	16	2.27	16.67
Anti-LGI1	1105	30	18	3	9	2.71	21.23
Anti-CASPR2	1105	20	15	0	5	1.81	13.89
Anti-AMPAR1–2	934	2	2	0	0	0.21	1.39
Anti-GABAbR	934	2	1	0	1	0.21	1.39
Total NSAb (NMDAR, LGI1, CASPR2, AMPAR, GABAbR)	1179	75	36	8	31	6.36	52.08
Anti-GAD65 (> 2000 UI/mL)	447	20	9	4	7	4.47	13.89
Onconeural	709	32	24	2	6	4.51	22.22
Anti-AQP4	568	19	16	0	3	3.35	13.19
Total	1849	144	83	14	47	7.79	100.00

Legend. S + = isolated serum positivity; CSF + isolated cerebrospinal fluid positivity; S/CSF + = both serum and CSF positivity.

Table 2
Patients with autoimmune encephalitis associated with NSAbs diagnosed in the period June 2013 – July 2018 and residents in Treviso (Tv) and Trento (Tn) provinces.

Padova-Treviso Lab 1st sample code	Pro-vinces	Sex / Age (at onset)	NSAb	Ab positivity in S / CSF / or both S and CSF	Presentation	CSF	EEG	Medio-temporal MR abnorma-lity	Tumor (other relevant comorbidities)	Immunotherapy	Follow up (months)
13,203	Tn	M / 60	Lgi1	S	Complex focal seizures	Normal	Temporal epileptic discharges	Yes	No (histiocytic necrotizing lymphadenitis)	St	80
13,346	Tn	M / 70	GlyR	S and CSF	Dysphagia, brainstem myoclonic disorder	Normal	Slow waves	No	No	St, PEX, IVIG; RTX	11
15,014	Tn	F / 69	Lgi1	S and CSF	Complex focal seizures	Normal	Bitemporal epileptic discharges	No	No	St, PEX, IVIG	13
16,333	Tn	M / 52	Caspr2	S	Confusion, amnesia, epilepsy	Normal	Bitemporal epileptic discharges	Yes	No	St, IVIG; AZA	46
17,067	Tn	F / 67	NMDAR	S	Status epilepticus	Not available	Status epilepticus	Yes	No	–	1 (death)
17,163	Tv	F / 23	NMDAR	CSF	Psychosis	Normal	Bitemporal epileptic discharges	No	Teratoma	St, IVIG; RTX, CP	36
17,210	Tv	M / 63	Lgi1	S	Generalized seizures	Mild protein increase	Normal	No	No	St; MMP	42
17,338	Tv	M / 58	Lgi1	S and CSF	Epileptic seizures, amnesia, behavioral changes	Normal	Normal	Yes	No	St, IVIG	18
17,390	Tn	F / 21	NMDAR	S and CSF	Psychosis	Mild pleocytosis	Bitemporal epileptic discharges	Yes	No	St; RTX	44
17,533	Tn	F / 47	Lgi1	CSF	Confusion, amnesia, epilepsy	Oligoclonal bands	Bitemporal epileptic discharges	Yes	No	St, IVIG	29
18,106	Tn	M / 58	Lgi1	CSF	Amnesia, confusion, epilepsy, sleep disorder	Normal	Slow waves	No	No	St, PEX; CP, RTX	9

Legend. St = steroids; IVIG = intravenous immunoglobulins; PEX = plasma exchange; RTX = rituximab; AZA = azathioprine; CP = cyclophosphamide; MMP = mycophenolate mofetil.

study reporting 5.3% overall positivity for neuroglial targets, applying a similar algorithm in unselected patients (Bien et al., 2020). Another study from South-West China reported a much higher rate of NSAb positivity (41%), suggesting that cases were selected on clinical grounds (Gu et al., 2019) (Table 3).

Reporting crude positivity rates of NSAb diagnosis among different populations and methodologies precludes proper comparison. Nevertheless, these data do suggest the presence of additional geographical factors including, for instance, different availability/access to diagnostic tests.

Even excluding non-specific VGKC-Abs (Lang et al., 2017), NSAbs diagnosis accounted for more than half of the neuroglial antibodies detected, similarly to the Bielefeld data (Bien et al., 2020). LGI1-Abs were the most common antibody, followed by NMDAR- and CASPR2-Abs. In other studies anti-NMDAR-Abs proved to be much more common (McCracken et al., 2017)(Gu et al., 2019), which is explainable, at least in part, by the presence of pediatric and non-Caucasian patients. Our data are in line with another Italian study (Iorio et al., 2020), and with the largest published German cohort, which also demonstrated the greater specificity of the LGI1-Abs compared to the NMDAR-Abs commercial assay (Bien et al., 2020) (Table 3).

The incidence of NSAE in adults in the provinces of Treviso and Trento was found to be 1.93/1,000,000 population per year (Table 4).

The first study to provide epidemiologic data on NSAE was

Table 3
Published studies on NSAb diagnostics.

	Padova-Treviso, Italy	Philadelphia, USA (McCracken et al., 2017)	Southwest China (Gu et al., 2019)	Bielefeld, Germany (Bien et al., 2020)
Total	1853	623	457	10,919
Period	07/2013–06/2018 (5 years)	01/2015–12/2015 (2 years)	01/2012–02/2018 (6 years)	12/2011–12/2015 (5 years)
Av. patients/year	**371**	311	91	2183
Antibodies tested and lab assays	Commercial IIF CBA (+/-TBA)	Commercial + In-House IIF CBA + TBA	Commercial IIF CBA	Commercial IIF CBA (+/-TBA)
No. positive (%)	**144 (7.8)**	96 (15.4)	189 (41.36)	576 (5.3)
Anti-NMDAR (No. positive and % of ab-positive patients)	**24 (16.7)**	67 (69.8)	153 (80.95)	67 (11.6)
Anti-LGI1 (No. positive and % of ab-positive patients)	**30 (21.2)**	5 (5.2)	9 (4.76)	81 (14.1)

Table 4
Published studies on NSAE epidemiology.

	Treviso-Trento (north-east Italy)	UK (Granerod et al., 2010)	Netherlands (van Sonderen et al., 2016)	Olmsted County, MN, USA (Dubey et al., 2018)	France (Hébert et al., 2020)
Study type / population / period (years)	Hospital-based / 1,427,318 / Jun 2013 – Jul 2018 (5)	Hospital –based / approx 5 million / 2005–2006 (2)	Population-based, nationwide LGI1-focused / approx. 17,000,000 / Oct 2014–Sept 2015 (1)	Population-based /155,285 / 1995–2015 (10)	Population-based nationwide / 66,992,699 (Rhône-Ain-Isère region: (3,798,135) / 2016–2018 (3)
NSAE incidence (per million/ year)	1.54	1.6 *	N.A.	0.6	1.8 (France) 3.6 (Rhône-Ain-Isère region)
LGI1-E incidence	0.84	N.A.	0.83	–	0.6

(*16 patients: 9 NMDAR, 7 VGKC)

conducted in UK (Granerod et al., 2010). Over a 2-year period, NSAbs were detected in 16 patients (9 NMDAR and 7 VGKC) with an estimated incidence of 1.6/1,000,000 persons per year.

In the epidemiologic study conducted in Olmsted County, Minnesota between 1995 and 2015, 24 cases of AE were diagnosed, 11 with neuroglial antibodies, mostly MOG- or GAD65-Abs (Dubey et al., 2018). Only two cases of NSAE were diagnosed, indicating an estimated incidence of 0.6/1,000,000 persons per year.

A more recent population-based epidemiologic study evaluated incidence rates of PNS and AE in France between 2016 and 2018 (Hébert et al., 2020). The estimated incidence in the Rhône-Ain-Isère reference region was 3.6/1,000,000 persons per year (NMDAR 0.9; LGI1 0.6).

Although commonly considered as a whole, AEs constitute a heterogeneous group of disorders. The AE diagnostic criteria provided by Graus and colleagues have an operational role in clinical practice and are not intended for epidemiologic analysis (Graus et al., 2016). We thus excluded possible or probable AE, focusing solely on NSAb–positive AE cases.

LGI1-encephalitis proved to be the most common type of NSAE in the adult population of Trento and Treviso provinces, paralleling data emerging from routine NSAb detection. Another Italian study supported similar findings, suggesting a role for genetic background (Iorio et al., 2020). The incidence of LGI1-encephalitis (0.84/1,000,000 persons per year) was similar to the annual incidence in the Netherlands (0.83) (van Sonderen et al., 2016) and slightly higher than in the French reference-center region of Lyon (0.6) (Hébert et al., 2020).

This study has several limitations. Firstly, it was retrospective; secondly the analysis of the frequencies and trends in NSAb diagnostics was not correlated with clinical data thus precluding the estimation of sensitivity and specificity. In addition we cannot exclude an underestimation of incidence due to hospitalization of residents outside the two provinces.

There is no gold standard for assessing NSAb validity. Diagnosis of NSAE is based not only on antibody results but also requires clinical ratings. It is essential to recognize the real incidence of these pathologies to appropriately design adequate therapeutic trials.

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