

# Epidemiology of paraneoplastic neurologic syndromes and autoimmune encephalitides in France

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## Abstract

### Objective

To determine the observed and expected incidence rates of paraneoplastic neurologic syndromes (PNSs) and autoimmune encephalitides (AEs) diagnosed in France between 2016 and 2018, we conducted a population-based epidemiologic study.

### Methods

Observed incidence rates were stratified by sex, age groups, region of care, year of diagnosis, and disease subgroups. National expected incidence rates were calculated based on rates obtained in the area directly adjacent to the Reference Center using a mixed Poisson model and compared with observed incidence rates.

### Results

Six hundred thirty-two patients with definite PNS or AE met the inclusion criteria. The observed incidence rate of definite PNS and AE in France was 3.2 per million person-years (CI<sub>95%</sub>: 2.9–3.4) compared with an expected incidence rate of 7.1 per million person-years (CI<sub>95%</sub>: 3.9–11.4). The national observed incidence rate for the antibody-positive AE subgroup increased from 1.4 per million person-years (CI<sub>95%</sub>: 1.2–1.7) in 2016 to 2.1 per million person-years (CI<sub>95%</sub>: 1.7–2.4) in 2018, thus surpassing the incidence rate of classical PNS (1.2 per million person-years [CI<sub>95%</sub>: 1.0–1.5]) of 2018.

### Conclusions

There was a significant widespread year-to-year increase in the incidence of diagnoses registered with the Reference Center for all subgroups of PNS and AE studied. The national observed incidence rate is likely underestimated due to underdiagnosis and underreporting.

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## Glossary

**AE** = autoimmune encephalitides; **CRC** = colorectal cancer; **LEMS** = Lambert-Eaton myasthenic syndrome; **PNS** = paraneoplastic neurologic syndrome; **SCLC** = small-cell lung cancer.

Paraneoplastic neurologic syndromes (PNSs) and autoimmune encephalitides (AEs) are neuroimmune disorders that are both characterized by the presence of autoantibodies that target the nervous system.<sup>1,2</sup> Even if PNSs and AE appear to be rare, their recognition is essential because immunomodulatory treatments have been associated with marked improvements and even resolution of symptoms in a significant proportion of cases.<sup>3–6</sup> Despite their associated human<sup>3</sup> and economic costs,<sup>7</sup> these neuroimmune disorders have seldom been the subject of epidemiologic studies. The annual incidence per million person-years has been estimated at 8.9 for PNS in Northeastern Italy,<sup>8</sup> 5 for antibody-positive AE in Olmsted County, MN,<sup>9</sup> 0.83 for leucine-rich glioma inactivated 1 (LGI1) encephalitis in the Netherlands,<sup>10</sup> and 0.9 to 2.2 for pediatric N-methyl-D-aspartic acid (NMDAR) encephalitis in the United Kingdom and Hong Kong.<sup>11,12</sup> All of these studies have reported year-to-year increases in incidence in a context of increased diagnostic abilities and improved recognition of clinical syndromes.<sup>9,11,12</sup>

The main objective of this study was to measure the incidence of PNS and AE and their subgroups registered with the French National Reference Center between 2016 and 2018 inclusively. The secondary objectives were to evaluate the regional heterogeneity in incidence of declaration and quantify underreporting by providing an expected incidence rate based on the predicted rates calculated for the area surrounding the Reference Center.

## Methods

### Population and patients

France has a population of 66,992,699 inhabitants (source: Institut national de la statistique et des études économiques [INSEE] January 1, 2019). The French National Reference Center for PNS and AE is located in Lyon, the second most populous metropolitan area of France. The Reference Center directly cares for patients diagnosed with PNS and AE in the surrounding Rhône-Ain-Isère region (3,798,135 inhabitants on January 1, 2019). In addition to clinical care, this center provides countrywide guidance via telemedicine and antibody testing for suspected cases of PNS or AE. Although it is conceivable that patients be diagnosed locally with commercially available diagnostic panels (thus bypassing reporting to the reference center), the share of such underreporting was felt to be small and was mitigated by agreements between the Reference Center and private providers of autoimmune testing for reporting antibody-positive cases. Clinical information on patients referred to the center or obtained through our partners was collected and kept in a database onsite.

Cases from the Reference Center database diagnosed in France between January 1, 2016, and December 31, 2018, that met the following criteria were included: (1) definite AE,<sup>2</sup> except for patients with negative or atypical antibody testing, or (2) definite PNS,<sup>1</sup> excluding cases of dermatomyositis, Lambert-Eaton myasthenic syndrome (LEMS), or with antibodies targeting P/Q-type voltage-gated calcium channel antibodies, SOX1, myelin oligodendrocyte glycoprotein, or aquaporin 4. Atypical antibody testing was defined as positive immunofluorescence with neuronal staining without target identification. Also excluded were all cases with missing biospecimens or missing information on location of care (figure e-1, [links.ww.com/NXI/A308](https://www.annals.org/lookup/suppl/doi:10.1093/annals/abaa038/-/dc1)). Antibody positivity was confirmed using at least 2 different techniques (i.e., tissue-based immunofluorescence and cell-based assay or Western blot/immunodot) according to the antibody type.<sup>13</sup> Both serum and CSF were tested whenever available. For specific antibodies (e.g., GAD65), other additional techniques (ELISA) were adopted, using serum titers >250 IU/mL as a cutoff.<sup>14</sup>

### Diagnostic classification

The cases included in this study were collectively referred to as definite PNS and AE—further emphasizing the exclusion of patients with negative/atypical antibody testing without an associated cancer. We used the following classification for subgroup analysis: (A) the PNS subgroup included patients who had a neurologic syndrome associated with a malignant tumor (including malignant thymoma but excluding teratoma) or who tested positive for a classic onconeural antibody (namely, anti-amphiphysin, -CV2/CRMP5, -Delta/Notch-like epidermal growth factor-related receptor, -Hu [ANNA1], -Ri [ANNA2], -Yo [PCA1], or -Ma2 antibody)<sup>1</sup>; (B) the classical PNS subgroup included only patients who tested positive for one of the aforementioned typical onconeural antibodies; (C) the antibody-positive AE subgroup included patients with an antibody typically associated with AE (anti-AK5, -alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid receptor [AMPA], -CASPR2, -dipeptidyl-peptidase-like protein 6, -LGI1, -D2R, -gamma aminobutyric acid-A receptor, -gamma aminobutyric acid-B receptor, -glycine receptor, -immunoglobulin-like cell adhesion molecule 5, -glutamic acid decarboxylase, -glial fibrillary acidic protein, -LGI1, -mGluR1, -mGluR5, or -NMDAR antibodies<sup>15,16</sup>) and having 2 of the 3 following criteria<sup>2</sup>: (1) subacute encephalopathy; (2) MRI with bitemporal T2 fluid attenuated inversion recovery abnormalities; and (3) CSF pleocytosis or EEG with epileptic or slow-wave activity involving the temporal lobes; and (D), (E), and (F) subgroups included patients who tested positive for, respectively, anti-NMDAR, -LGI1, and -Hu antibodies. Patients who tested positive for an AE antibody and were diagnosed with a concomitant cancer were referred to as paraneoplastic AE and were included concurrently into the PNS and antibody-positive

AE subgroups. All cancer diagnoses included occurred within 5 years of symptom onset for classical PNS and 2 years for other PNS.<sup>1</sup> For patients testing positive to more than 1 onconeural antibody, the antibody the most consistent with their clinical presentation was assigned.

### Patients' characteristics

For patients included in the study, the following characteristics were extracted from the database: age, sex, associated neoplasm, region of care, year of diagnosis, and results of antibody panel testing. We then described these characteristics for each subgroup—using absolute and relative frequency for qualitative characteristics, and median and range for quantitative characteristics. We described the distribution of cases using sex-age pyramids. Testing for all aforementioned antibodies was available throughout the study period, except for glial fibrillary acidic protein, which became available in 2017.

### Estimate and modeling of incidence rates

We stratified the cases and corresponding population strata by sex, age group, region of care, and year of diagnosis. We then calculated the person-years spent at risk—the average size of the population estimated between January 1st of that year and the following year<sup>17</sup>—in each stratum using population data from the INSEE. We used the region of care as a surrogate for region of residence. Because all regions of France, with the exception of Corse, can count on at least 1 tertiary care center within their borders, the tendency for patients to seek care outside of their region of residence was felt to be minimal. We tested the soundness of this premise for the Rhône-Ain-Isère region—which was assumed to have the highest rate of non-resident diagnosis due to the location of the national reference center within its walls—and we found that only 12% of the patients diagnosed within the Rhône-Ain-Isère region were nonresidents. We estimated crude incidence rates by sex, age group, region, year of diagnosis, and for the entire French population over the period 2016–2018 with 95% CIs built using an exact method based on a Poisson distribution.

We used log-linear mixed models to model the case count according to sex and age groups. We put a random intercept on the variable region, specified an age-sex interaction as fixed effect, and used the logarithm of the number of person-years as an offset.<sup>18</sup> To account for nonlinearity, we modeled the age effect using a cubic spline with 3 knots.<sup>19</sup> We used the predicted relative incidence rates for the regions to quantify the interregional heterogeneity of the incidence rate taking into account the heterogeneity due to sample size variability and adjusting for sex and age. These predicted relative incidence rates corresponded to the exponential of the best linear unbiased predictors of the mixed models and were relative to the mean incidence rate. We used maps to represent the national distribution of the relative incidence rates.

We also used a model with year of diagnosis specified as fixed and random effect to investigate the effect of the variable year of diagnosis on the incidence rates.

### Expected number of cases and incidence rates in France

We considered the Rhône-Ain-Isère region the reference area in terms of completeness of case declaration because of its proximity to the Reference Center. We estimated the expected number of cases of definite PNS and AE over the period 2016–2018 by applying the predicted incidence rates obtained from the mixed model for the reference area to the person-years of each stratum of the French population. We aggregated that the expected numbers of cases were by sex, 4 age groups (0–19, 20–39, 40–59, and ≥60 years), and the entire French population. The expected incidence rates corresponded to the ratio of the expected number of cases to the number of person-years. We obtained 95% CIs for the expected numbers of cases and incidence rates using a bias-corrected and accelerated bootstrap method.

We conducted all statistical analyses with R version 3.6.0 (R Core Team, Vienna, 2019), using the `glmmPQL` function in package `NLME`<sup>18</sup> for the mixed Poisson models. The packages `ggplot2`,<sup>20</sup> `rgdal`,<sup>21</sup> and `broom`<sup>22</sup> were used for mapping the relative incidence rates.

### Standard protocol approvals, registrations, and patient consents

The Ethics Review Board of the Hospices Civils de Lyon (19–85) approved this study, which is registered with ClinicalTrials.gov (No. NCT03957616). The French Commission nationale de l'informatique et des libertés also approved the study for data collection (Commission nationale de l'informatique et des libertés [CNIL] authorization number: 19–147).

### Data availability

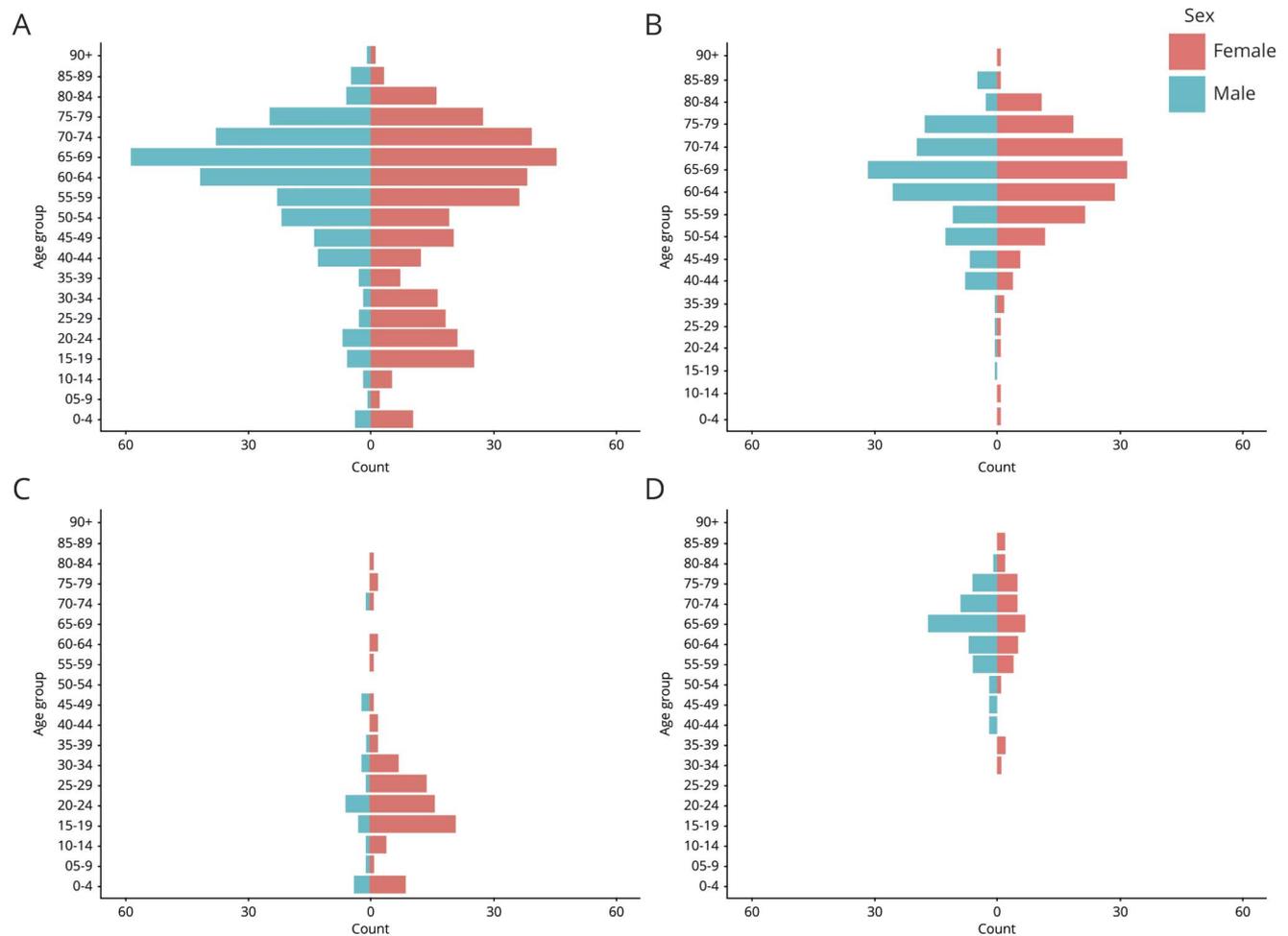
Anonymized data will be shared by request from any qualified investigator for purposes of replicating procedures and results.

## Results

### Definite PNS and AE

Among 13,442 referred cases, 632 patients had a diagnosis of definite PNS or AE: 175/3,376 (5.1%) in 2016, 218/4,445 (5.0%) in 2017, and 239/5,621 (4.3%) in 2018. The distribution of cases showed a bimodal age distribution with a first peak at ages 15–19 years (predominantly female patients with antibody-positive AE) and a second higher peak at ages 65–69 years (high proportion of males, predominantly PNS cases) (figure 1A). As hypothesized, the most commonly identified antibodies were anti-NMDAR, followed by anti-LGI1, and anti-Hu (table 1; figure e-2, [links.lww.com/NXI/A309](https://links.lww.com/NXI/A309)). The proportion of females among Yo-, NMDAR-, and glutamic acid decarboxylase-positive patients was significantly above 50%, whereas it was below 50% among LGI1-, Ma2-, and CASPR2-positive patients (figure 2). Fifteen (2%) patients tested positive for 2 antibodies: 9 had dual antibodies against CV2 and Hu, 5 against LGI1 and CASPR2, and 1 against CV2 and Yo.

**Figure 1** Sex-age pyramids by subgroup



(A) Definite paraneoplastic neurologic syndromes and autoimmune encephalitides. (B) Paraneoplastic neurologic syndromes. (C) NMDAr-positive patients. (D) LGI1-positive patients.

Among the patients with definite PNS or AE diagnosis, 243 (38.4%) had an associated diagnosis of cancer. In descending order, these cancers were lung cancer (59/243, 24%, small-cell lung cancers [SCLCs], and 47/243, 19%, non-small-cell lung cancers), gynecologic cancers (34/243, 14%), breast cancer (29/243, 12%), malignant thymoma (15/243, 6%), lymphoma (13/243, 5%), renal cell carcinoma (11/243, 5%), and prostate cancer (10/243, 4%). Less than 10 cases were found for each of leukemia, colorectal cancer (CRC), testicular, thyroid, skin, neuroendocrine, pancreatic, liver, head and neck, and bladder cancers.

The crude incidence rates of definite PNS or AE were 3.2 per million person-years ( $CI_{95\%}$ : 2.9–3.4; the incidence rates for the different subgroups are shown in table 2). For all subgroups, a yearly increase in crude incidence rates was observed. The highest crude incidence rates were seen in overseas regions of Martinique and Guadeloupe, followed by the Rhône-Ain-Isère region (table e-1, [links.lww.com/NXI/A310](https://links.lww.com/NXI/A310)). After modeling of incidence rates, significant regional heterogeneity remained (interregional SD = 0.26, figure 3). The Rhône-Ain-Isère region (site of the

National Reference Center) had the highest predicted relative incidence rate (i.e., 2 times the mean rate), followed by Aquitaine (1.3x) and Martinique and Guadeloupe (1.2x). The mean incidence rate increased significantly with the year of diagnosis (relative year-on-year incidence rate = 1.20x,  $CI_{95\%}$  = 1.18–1.22).

### Expected numbers of cases and incidence rates

We estimated the crude incidence rate of definite PNS and AE in the Rhône-Ain-Isère region at 7.5 per million person-years ( $CI_{95\%}$ : 6.0–9.3). We estimated the expected number of cases in France at 1,411 ( $CI_{95\%}$ : 774–2,272) and the national incidence rate of definite PNS and AE at 7.1 per million person-years ( $CI_{95\%}$ : 3.9–11.4). We estimated the expected national rate of definite PNS and AE per million person-years among females at 7.7 ( $CI_{95\%}$ : 2.3–10.1) and 6.4 among males ( $CI_{95\%}$ : 2.6–11.9). Looking at age groups, we estimated the expected national incidence rates per million person-years at 2.5 ( $CI_{95\%}$ : 0.9–5.6) in the 0–19 age group, 3.1 ( $CI_{95\%}$ : 1.2–6.7) in the 20–39 age group, 8.3 ( $CI_{95\%}$ : 3.4–16.7) in the 40–59 age group, and 13.9 ( $CI_{95\%}$ : 5.5–28.9) in patients older than 60 years.

**Table 1** Patients' characteristics

Characteristic	Definite PNS and AE	PNS	Antibody-positive AE
All patients, n (%)	632	317	355
Female patients, n (%)	357 (56.5)	171 (53.9)	202 (56.9)
Age, median (range)	62.1 (0–94)	65.9 (0–93)	54.9 (0–94)
Associated cancers, n (%) <sup>a</sup>	243 (38.5)	243 (77%)	40 (11.3)
<b>Antibodies, n (%)</b>			
Anti-NMDAr	106 (16.7)	1 (0.3)	106 (33.0)
Anti-LGI1	85 (13.3)	11 (3.4)	85 (26.5)
Anti-Hu	84 (13.2)	84 (26.2)	0 (0.0)
Negative/atypical	78 (12.3)	78 (24.3)	0 (0.0)
Anti-GAD	71 (11.2)	4 (1.2)	71 (2.2)
Anti-Yo	37 (5.9)	37 (11.7)	0 (0.0)
Anti-CASPR2	37 (5.8)	9 (2.8)	37 (11.5)
Anti-CV2	31 (4.9)	31 (9.7)	0 (0.0)
Anti-GFAP	21 (3.3)	1 (0.6)	21 (6.5)
Anti-Ma2	19 (3.0)	19 (5.9)	0 (0.0)
Anti-GABA <sub>B</sub> R	18 (2.8)	10 (5.6)	18 (5.6)
Anti-DNER	12 (1.9)	12 (3.7)	0 (0.0)
Anti-Ri	11 (1.7)	11 (3.4)	0 (0.0)
Others	22 (3.5) <sup>b</sup>	9 (2.5) <sup>c</sup>	16 (5.0) <sup>d</sup>

Abbreviations: AE = autoimmune encephalitis; DNER = Delta/Notch-like epidermal growth factor-related receptor; GABA<sub>B</sub>R = gamma aminobutyric acid-B receptor; GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein; LGI1 = leucine-rich glioma inactivated 1; NMDAr = N-methyl-D-aspartic acid; PNS = paraneoplastic neurologic syndrome.

<sup>a</sup> Excluding 22 cases of teratomas.

<sup>b</sup> AK5: 3; AMPAR: 4; amphiphysin: 5; IgLON5: 3; mGluR1: 3; mGluR5: 1; GlyR: 1; GABA<sub>A</sub>: 1; and D2R: 1.

<sup>c</sup> AMPAR: 2; amphiphysin: 5; IgLON5: 1; and mGluR5: 1.

<sup>d</sup> AK5: 3; AMPAR: 4; GABA<sub>A</sub>: 1; GlyR: 1; IgLON5: 3; mGluR1: 3; and mGluR5: 1.

## Paraneoplastic neurologic syndromes

Of the 317 patients diagnosed with PNS, 195 met the criteria for classical PNS, and 82 had atypical/negative testing for antibodies with associated cancers. Forty patients were diagnosed with paraneoplastic AE (figure e-1, [links.lww.com/NXI/A308](https://links.lww.com/NXI/A308)). The proportion of female patients within the PNS subgroup—slightly above 50%—remained relatively constant throughout all age groups (figure 1B). The most commonly diagnosed tumor types were lung cancer (32% of all cancer cases), gynecologic cancer (15%), and breast cancer (14%).

The 70–74 age group had the highest crude incidence rate of PNS: 5.7 per million person-years (CI<sub>95%</sub>: 4.3–7.6), whereas no cases were recorded in the 5–9 age group (CI<sub>95%</sub>: 0.0–0.3 per million person-years). After modeling of incidence rates, the incidence of PNS showed a significant heterogeneity between regions (SD of the distribution of the random intercept = 0.35).

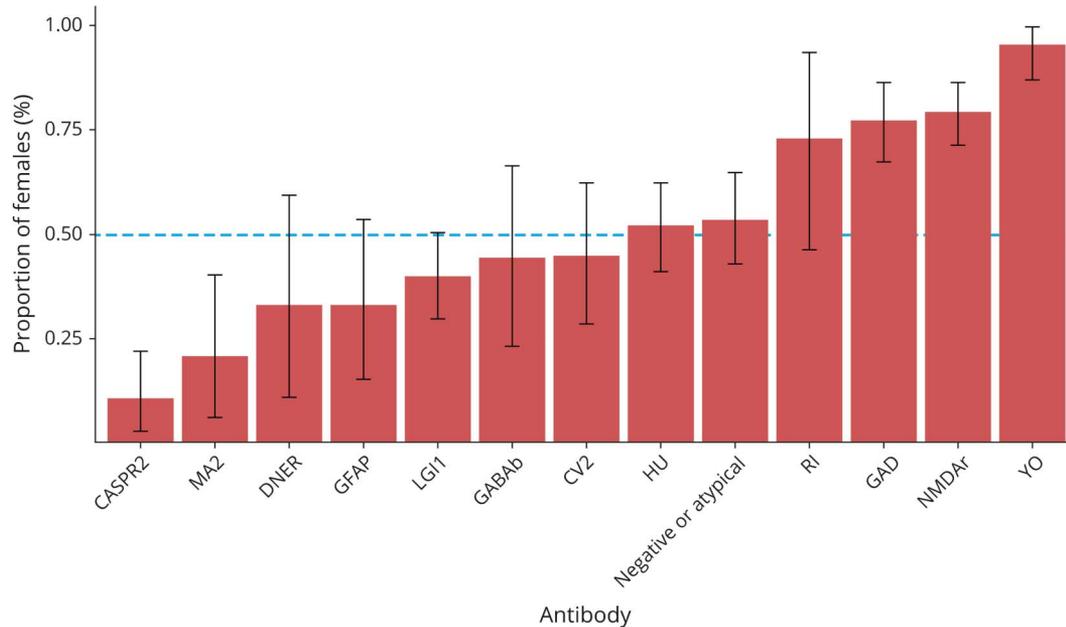
The antibodies detected in the classical PNS subgroup were Hu (84/195, 43%), Yo (37/195, 19%), CV2/CRMP5 (31/185, 15%),

Ma2 (19/195, 9%), Delta/Notch-like epidermal growth factor-related receptor (12/195, 6%), Ri (11/195, 5%), and amphiphysin (5/195, 2%). The median age of the patients with classical PNS was 66.1 years (range: 0–93 years). Of the 84 Hu-positive cases, 43 (52%) were female, and their median age was 66.5 years (range: 41–93 years), near the median age of the overall PNS subgroup. Cancer was present in 62 patients (74%) of the Hu-positive subgroup: 34 SCLC, 20 NSCL, 2 prostate cancers, 1 breast cancer, 1 CRC, 1 bladder cancer, and 1 uterine cancer.

## Antibody-positive autoimmune encephalitis

Within the antibody-positive AE subgroup, the sex distribution differed markedly according to age: while a female predominance was noted in patients younger than 50 years, males were more commonly diagnosed in patients older than 50 years. Of the 40 patients with paraneoplastic AE (11.3% of the total antibody-positive subgroup; table 1), there were 11 with gamma aminobutyric acid-B receptor, 11 with anti-LGI1, and 9 with CASPR2 antibodies. Compared with overall antibody-positive AE cases, patients with paraneoplastic AE were older

**Figure 2** Proportion of females by antibody type



(median age: 64.8 vs 54.9 years;  $p < 0.001$ ) and less likely to be female (40% vs 57%;  $p = 0.03$ ). The incidence rate of antibody-positive AE again showed significant interregional heterogeneity (SD of the distribution of random intercept = 0.32).

The median age of the NMDAr subgroup was 22.3 years (range: 0–80 years; figure 1C), significantly lower than the median age of the whole antibody-positive AE subgroup (vs 54.9 years;  $p < 0.005$ ). In this subgroup, 79% were females, which is also significantly higher than the percentage in the whole antibody-positive AE subgroup (57%;  $p < 0.005$ ). Twenty-one cases (20%) had teratoma, and 1 had Hodgkin lymphoma.

The LGI1-positive patients were older (median age: 67.4 vs 54.9 years; range: 33–86,  $p < 0.001$ ; figure 1D) and more likely to be males (males = 40% vs 57%;  $p = 0.005$ ) than the whole antibody-positive AE subgroup. Only 11 cases of cancer (13%) were found in these patients (6 malignant thymomas, 3 prostate cancer, 1 breast cancer, and 1 lung cancer).

## Discussion

We report on the epidemiologic features of PNS and AE diagnosed on the French territory and registered with the French National Reference Center between 2016 and 2018. Despite widespread advances made in the recognition and referral of these disorders, the discrepancy between the high incidence rates observed in the immediate vicinity of the Reference Center and the rest of France suggests that

underdiagnosis and underreporting still exist and highlights the need for uniform diagnostic procedures on a national scale. The regional heterogeneity in reported incidence rates may be partially explained by a combination of region-dependent underrecognition of these disorders, varying exhaustiveness in reporting, border effects with some university health centers located close to regional borders, and differences in referral patterns. Differences in regional racial composition are also a potential factor of heterogeneity: we indeed found higher crude incidence rates of definite PNS and AE in Martinique and Guadeloupe, regions with high proportions of inhabitants with African ancestry. This is akin to results by Dubey et al.<sup>9</sup> who reported higher incidence rates of AE among Blacks in Olmsted County, MN. Finally, the contribution of geographic factors to regional incidence heterogeneity was felt to be minimal given the absence of clear regional clustering (figure 3).

The crude incidence rates of antibody-positive AE (3.6 per million person-years) and PNS (4.1 per million person-years) in Rhône-Ain-Isère region were lower than rates found in, respectively, Olmsted County (5.0 per million person-years)<sup>9</sup> and Northeastern Italy (8.9 per million person-years).<sup>8</sup> These differences more likely reflect the increased challenge of achieving exhaustiveness in larger populations rather than true differences in incidence. Even when considering the area to the Rhone-Ain-Isère region only, the population at risk was 3,798,135 vs 155,285 for Olmsted County and 983,190 for Northeastern Italy.<sup>8,9</sup> Another potential cause of this lower incidence rate is the exclusion of patients with certain PNS (dermatomyositis and LEMS) and those harboring antibodies targeting P/Q-type voltage-gated calcium channel antibodies, SOX1, myelin oligodendrocyte glycoprotein, or aquaporin 4.

**Table 2** Incidence rates of PNS and AE in France and Rhône-Ain-Isère region, 2016 to 2018

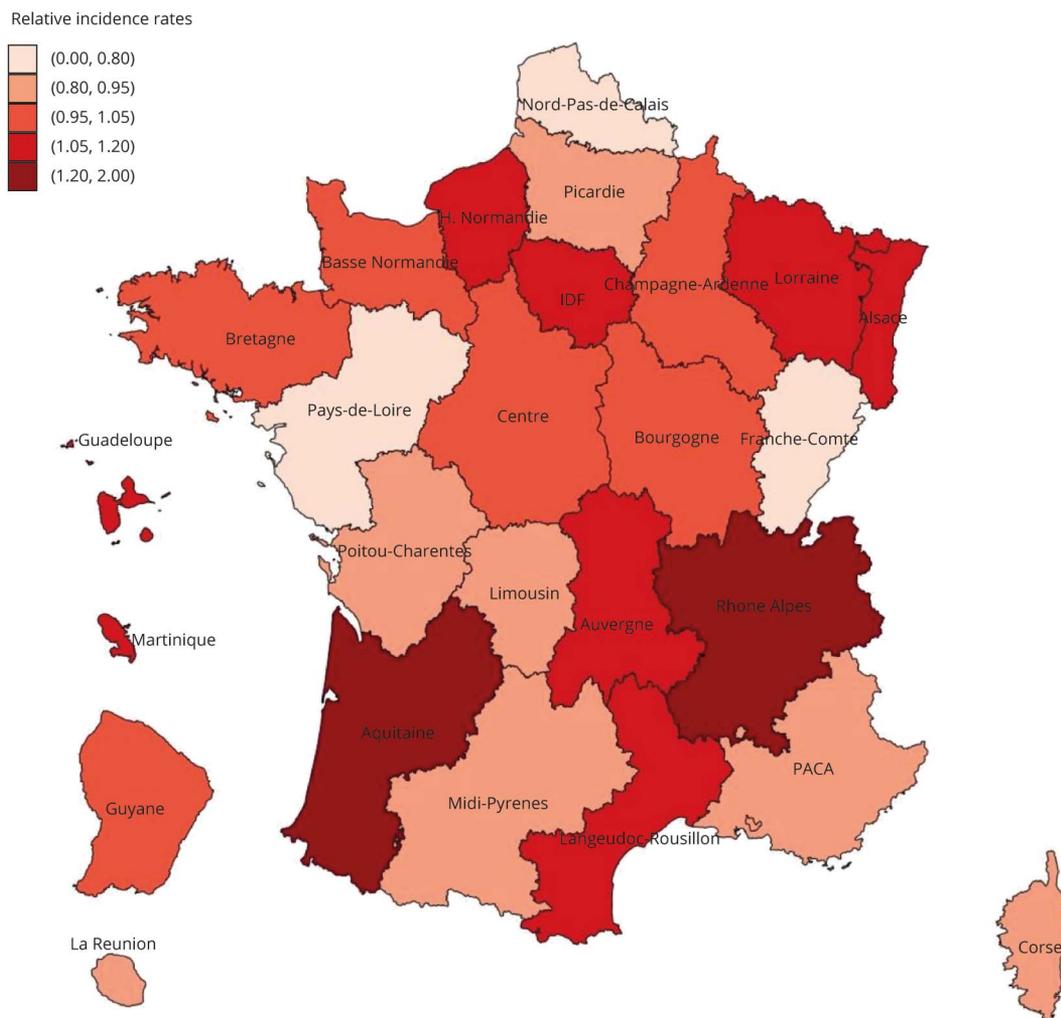
Subgroup and period	Whole France		Rhône-Ain-Isère region	
	Cases, n	Crude incidence <sup>a</sup> (95% CI)	Cases, n	Crude incidence <sup>b</sup> (95% CI)
<b>Definite PNS and AE</b>				
2016	175	2.6 (2.3–3.1)		
2017	218	3.3 (2.9–3.7)		
2018	239	3.6 (3.1–4.1)		
2016–2018	632	3.2 (2.9–3.4)	85	7.5 (6.0–9.3)
<b>PNS</b>				
2016	94	1.4 (1.1–1.7)		
2017	114	1.7 (1.4–2.0)		
2018	113	1.7 (1.4–2.0)		
2016–2018	317	1.6 (1.4–1.8)	46	4.1 (3.0–5.4)
<b>Antibody-positive AE</b>				
2016	95	1.4 (1.2–1.7)		
2017	121	1.8 (1.5–2.2)		
2018	139	2.1 (1.7–2.4)		
2016–2018	355	1.8 (1.6–2.0)	41	3.6 (2.6–4.9)
<b>Classical PNS</b>				
2016	52	0.8 (0.6–1.0)		
2017	68	1.0 (0.8–1.2)		
2018	82	1.2 (1.0–1.5)		
2016–2018	199	1.0 (0.9–1.1)	19	1.7 (1.0–2.6)
<b>Hu</b>				
2016	21	0.3 (0.2–0.5)		
2017	31	0.5 (0.3–0.7)		
2018	31	0.5 (0.3–0.7)		
2016–2018	83	0.4 (0.3–0.5)	11	1.0 (0.5–1.7)
<b>NMDAr</b>				
2016	28	0.4 (0.3–0.6)		
2017	35	0.5 (0.4–0.7)		
2018	43	0.6 (0.5–0.9)		
2016–2018	106	0.5 (0.4–0.6)	10	0.9 (0.4–1.6)
<b>LGI1</b>				
2016	24	0.3 (0.2–0.5)		
2017	23	0.4 (0.2–0.5)		
2018	38	0.6 (0.4–0.8)		
2016–2018	85	0.4 (0.3–0.5)	7	0.6 (0.2–1.3)

Abbreviations: AE = autoimmune encephalitides; LGI1 = leucine-rich glioma inactivated 1; NMDAr = N-methyl-D-aspartic acid; PNS = paraneoplastic neurologic syndrome.

<sup>a</sup> The numbers of person-years spent at risk for whole France were 66,439,735 in 2016; 66,574,069 in 2017; 66,676,327 in 2018; and 199,690,131 for period 2016–2018.

<sup>b</sup> The number of person-years spent at risk for Rhône-Ain-Isère for period 2016–2018 was 11,291,348.

**Figure 3** Maps of relative incidence rates of definite paraneoplastic neurologic syndromes and autoimmune encephalitides in France for 2016–2018



The fact that antibody-positive AE is now at least as commonly diagnosed as PNS suggests that there was a rapid, albeit heterogeneously distributed, heightened awareness of the condition. In fact, classical PNS—a group whose antibodies were described in the 1980s and 1990s—now represents only about a third of all definite PNS and AE cases. Part of the increased incidence seen in this subgroup may be attributable to more widespread use of immune checkpoint inhibitors in oncological practice, as already observed for specific central<sup>23</sup> and peripheral nervous system disorders,<sup>24</sup> including anti-Hu<sup>25</sup> and anti-Ma2-associated syndromes.<sup>26</sup>

To address the aforementioned limitations of exhaustiveness and referral patterns, future incidence studies should strengthen interhospital collaborations and ensure increased reporting of these conditions to the National Reference Center in Lyon. Including information on the location of residence of the patients would allow for a more in-depth analysis of the possible role of geographic factors on the incidence of PNS and AE.

The population-based design of this study showed a relatively accurate epidemiologic picture. We hope that this study will lead to increased recognition and reporting of these neuro-immune disorders in regions of France with lower rates of declaration, possibly through targeted educational activities. Our data will serve as a comparator for future studies of incidence of PNS and AE, monitoring their incidence in space and time—concurrently with improvements in clinicians’ diagnostic capabilities.<sup>26</sup>

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## Disclosure

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## Publication history

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<b>Benjamin Riche, PhD</b>	Hospices Civils de Lyon, Lyon, France	Conception and design of the study; analysis of the data; and drafting of the manuscript
<b>Alberto Vogrig, MD</b>	Hospices Civils de Lyon, Lyon, France; Université Claude Bernard Lyon 1, Lyon, France	Acquisition of the data and revision of the manuscript for important intellectual content
<b>Sergio Muñoz-Castrillo, MD</b>	Hospices Civils de Lyon, Lyon, France; Université Claude Bernard Lyon 1, Lyon, France	Revision of the manuscript for important intellectual content
<b>Bastien Joubert, MD</b>	Hospices Civils de Lyon, Lyon, France; Université Claude Bernard Lyon 1, Lyon, France	Revision of the manuscript for important intellectual content
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<b>Véronique Rogemond, PhD</b>	Hospices Civils de Lyon, Lyon, France; Université Claude Bernard Lyon 1, Lyon, France	Acquisition of the data and revision of the manuscript for important intellectual content
<b>Dimitri Psimaras, MD</b>	Groupe Hospitalier Pitié-Salpêtrière, Paris, France; Université Pierre et Marie Curie-Paris 6, Paris, France	Revision of the manuscript for important intellectual content

## Appendix (continued)

Name	Location	Contribution
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<b>Jérôme Honnorat, MD, PhD</b>	Hospices Civils de Lyon, Lyon, France; Université Claude Bernard Lyon 1, Lyon, France	Conception and design of the study; acquisition of the data; drafting of the manuscript; and revision of the manuscript for important intellectual content

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