eTable 1. Annual incidence of anti-NMDAR encephalitis			
Year	No. of anti-NMDAR encephalitis patients	Incidence/million (95% CI)	No. of Dutch inhabitants
2015 (May-Dec)	14	1.24 (0.77-1.89) *	16,900,726
2016	17	1.00 (0.58-1.60)	16,979,120
2017	26	1.52 (0.99-2.23)	17,081,507
2018	10	0.58 (0.28-1.07)	17,181,084
2019	12	0.69 (0.36-1.21)	17,282,163
2015 - 2019	79	1.00 (0.62-1.59) **	17,098,077

* The incidence rate of 2015 was extrapolated to a whole year for correct incidence numbers.

** Based on 4 years and 8 months, as 2015 numbers were available for 8 months only.

eTable 2. Patient characteristics of all Dutch anti-NMDAR encephalitis patients (n=126)	
Gender, female	96 (76%)
Age of onset (median, IQR, range)	24 (17-38, 1-86)
<12	16 (13%)
12-17	23 (18%)
18-24	26 (20%)
25-34	27 (21%)
35-44	10 (8%)
45-54	3 (2%)
55-64	10 (8%)
65-74	7 (6%)
>75	4 (3%)
Onset to diagnosis, days (median, IQR, range)	26 (16-53, 4-5845)
Symptoms	
Behavioral changes	118 (94%)
Cognitive decline	110 (87%)
Speech problems	80 (64%)
Seizures	83 (66%)
Movement disorders	79 (63%)
Awareness problems	59 (47%)
Autonomic symptoms	52/125 (41%)
Hypoventilation	31 (25%)
Sleep disorders	55/124 (44%)
Hospital admission	120 (95%)
Hospital stay, days (median, IQR, range)	56 (27-86, 2-551)
ICU admission	61 (48%)
ICU stay, days (n=56; median, IQR, range)	29 (4-51, 1-307)
Ancillary testing	
CSF abnormal	103/121 (85%)
WBC elevated	92/121 (76%)
WBC (median, IQR, range)	18 (5-53, 0-267)
Antibody titer serum (n=102; median, IQR, range)	1:400 (1:200-1:1600, negative-1:12800)
Antibody titer CSF (n=104; median, IQR, range)	1:32 (1:8-1:128, negative-1:2048)
Seronegative	15/109 (14%)
MRI AIE related abnormalities [±]	29 (23%)
EEG abnormal	98/110 (89%)
Posterior rhythm abnormal	32/95 (34%)
Tumor	33/123 (27%)
Teratomas	24 (73%)
Carcinomas	9 (27%)
Post-HSV	13 (10%)
Immunotherapy	
First-line immunotherapy	123 (98%)
IV methylprednisolone	115/125 (92%)
IV immunoglobulins	99/125 (79%)
Plasma exchange	13/124 (11%)

Second-line immunotherapy	51 (41%)
Rituximab	46 (37%)
Cyclophosphamide	20 (16%)
Onset to first-line IT, days (median, IQR, range)	21 (11-45, 1-510)
Failure to first-line immunotherapy *	67/121 (55%)
Onset to improvement, days (n=114; median, IQR, range)	46 (29-89, 1-974)
First-line IT to improvement, days (n=109; median, IQR, range)	20 (7-41, -383-774) [∞]
Second-line IT to improvement, days (n=49; median, IQR, range)	14 (3-31, -420-344) [∞]
Outcome	
mRS max (n=126; median, IQR, range)	4 (3-5, 2-5)
mRS start IT (n=123; median, IQR, range)	4 (3-5, 2-5)
mRS 6 weeks (n=126; median, IQR, range)	3 (3-5, 0-6)
mRS 4 months (n=125; median, IQR, range)	3 (2-3, 0-6)
mRS 6 months (n=121; median, IQR, range)	2 (1-3, 0-6)
mRS 8 months (n=116; median, IQR, range)	2 (1-3, 0-6)
mRS 12 months (n=114; median, IQR, range)	2 (1-3, 0-6)
mRS 18 months (n=102; median, IQR, range)	1 (1-2, 0-6)
mRS 24 months (n=92; median, IQR, range)	1 (1-2, 0-6)
mRS last FU (median, IQR, range)	1 (0-2, 0-6)
Time to mRS 2, months (median, IQR, range)	5 (2-10, 0- not achieved)
Good mRS at 12 months	87/118 (74%)
FU, months (median, IQR, range)	27 (15-45, 2-180)
Good mRS at last FU	97/125 (78%)
Relapse	22 (18%)
Deceased	11 (9%)

Abbreviations: IQR = interquartile range, ICU = intensive care unit, CSF = cerebrospinal fluid, WBC = white blood cells count, MRI = magnetic resonance imaging, EEG = electroencephalogram, HSV = herpes simplex virus, IT = immunotherapy, mRS = modified Rankin scale, FU = follow-up.

Data are n (%), n/n (%), or median (interquartile range, range).

[±] AIE related abnormalities included T2/flair hyperintensy mesiotemporal or thalamus region.

***** Failure to first-line immunotherapy was defined as no clinical improvement within two weeks after start of treatment. Not all patients with first-line failure were treated with second-line therapy (mostly patients with onset <2012, early dead or children).

[∞] Nine patients showed clinical improvement before start of first-line immunotherapy, 7 of whom within 26 days prior to treatment. Six patients showed clinical improvement before start of second-line therapy. All were not completely recovered for which immunotherapy was administered.

eTable 3. Serostatus in anti-NMDAR encephalitis (n=109)			
	Seronegative (n = 15)	**Seropositive (n = 94)**	**p value**
Gender, female	11 (73%)	71 (76%)	1.00
Age of onset (mean, SD)	35 (22-67, 5-75)	23 (17-32, 1-86)	**0.016**
Onset to diagnosis, days (median, IQR, range)	23 (11-40, 5-179)	29 (16-54, 4-5845)	0.35
Symptoms			
Behavioral changes	13 (87%)	89 (95%)	0.25
Cognitive decline	12 (80%)	85 (90%)	0.37
Speech problems	7 (47%)	64 (68%)	0.11
Seizures	9 (60%)	63 (67%)	0.59
Movement disorders	6 (40%)	62 (66%)	0.054
Awareness problems	5 (33%)	47 (50%)	0.28
Autonomic symptoms	5 (33%)	44/93 (47%)	0.41
Hypoventilation	4 (27%)	21 (22%)	0.74
Sleep disorders	6 (43%)	44/92 (47%)	0.57
Number of symptoms (median, IQR, range)	4 (2-7, 1-7)	6 (4-7, 2-9)	0.10
Hospital admission	14 (93%)	91 (97%)	0.45
Hospital stay, days (median, IQR, range)	49 (18-93, 2-143)	57 (29-94, 3-551)	0.59
ICU admission	7 (47%)	45 (48%)	0.93
ICU stay, days (median, IQR, range)	19 (2-70, 1-71)	28 (4-50, 1-307)	0.47
Ancillary tests			
CSF abnormal	15 (100%)	75/90 (83%)	0.12
WBC elevated	15 (100%)	64/90 (71%)	**0.020**
WBC (median, IQR, range)	20 (10-54, 6-107)	14 (5-53, 0-267)	0.34
Total protein elevated	6 (40%)	16/86 (19%)	0.064
Antibody titer CSF (median, IQR, range)	1:8 (1:2-1:32, 1:2-1:128)	1:64 (1:16-1:256, negative-2048)	**0.0034**
MRI abnormalities AIE related	6 (40%)	15/90 (17%)	0.073
EEG abnormal	10/12 (83%)	77/85 (91%)	0.61
Posterior rhythm abnormal	1/9 (11%)	25/72 (34%)	0.26
Tumor	2 (13%)	26/91 (29%)	0.34
Teratomas	0	19	
Carcinomas	2 ±	7 ±±	
Post-HSV	2 (13%)	9 (10%)	0.65
Immunotherapy			
First-line immunotherapy	14 (93%)	93 (99%)	0.26
Onset to first-line IT, days (median, IQR, range)	25 (15-36, 3-172)	21 (10-51, 2-307)	0.67
Failure of first-line IT *	7/14 (50%)	52/91 (57%)	0.62
Second-line immunotherapy	5 (33%)	42 (45%)	0.58
Outcome			
Onset to improvement, days (median, IQR, range)	37 (29-70, 1-366)	49 (33-90, 7-974)	0.26
mRS max (median, IQR, range)	4 (4-5, 2-5)	4 (3-5, 3-5)	0.73
mRS at 12 months (median, IQR, range)	2 (1-3, 0-6)	2 (1-2, 0-6)	0.56
Good mRS after 1 year	8/14 (57%)	66/88 (75%)	0.16
Good mRS at last FU	11/15 (73%)	72/93 (76%)	0.75

Relapse	3 (20%)	18 (19%)	1.00
Deceased	1 (7%)	8 (9%)	1.00

Abbreviations: SD = standard deviations, IQR = interquartile range, ICU = intensive care unit, CSF = cerebrospinal fluid, WBC = white blood cells count, MRI = magnetic resonance imaging, EEG = electroencephalogram, HSV = herpes simplex virus, IT = immunotherapy, mRS = modified Rankin scale, FU = follow-up.

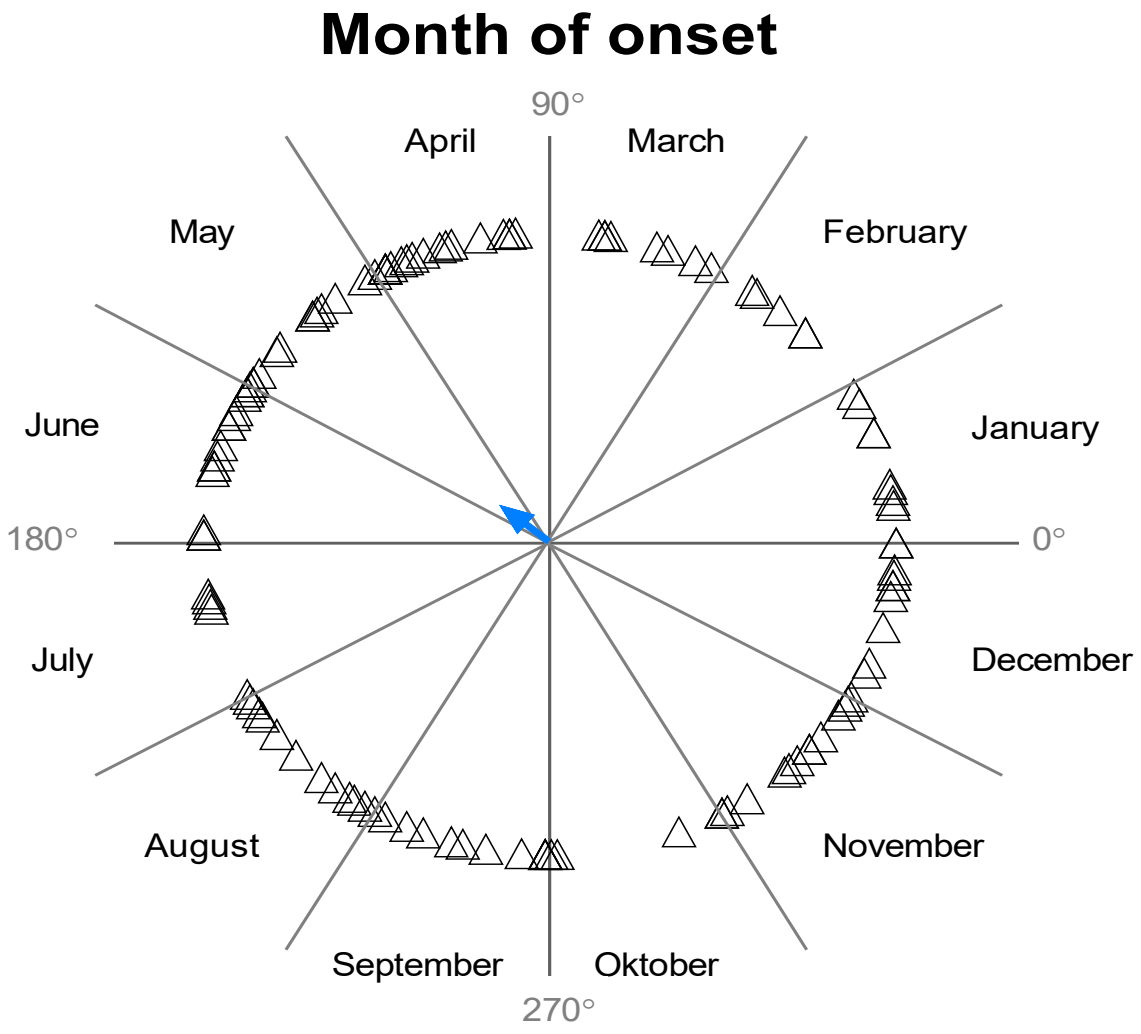
Data are n (%), n/n (%), mean (SD), or median (interquartile range, range).

[±] one small cell lung carcinoma and one metastatic esophageal carcinoma.

[±±] three small cell lung carcinoma, one colon carcinoma, one Merkel cell carcinoma, one endometrial carcinoma, one Hodgkin lymphoma.

***** Failure to first-line immunotherapy was defined as no clinical improvement within two weeks after start of treatment.

eFigure 1. Seasonal pattern in anti-NMDAR encephalitis



The figure represents the month of onset of all included anti-NMDAR encephalitis patients. Each square is one patient, showing a predominance of onset in May and June. Circular direction would aim at May 24 ($Z=1.80$, $p < 0.20$).

eFigure 2. Clinical outcome at follow-up