THE LANCET Neurology

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary figures and tables

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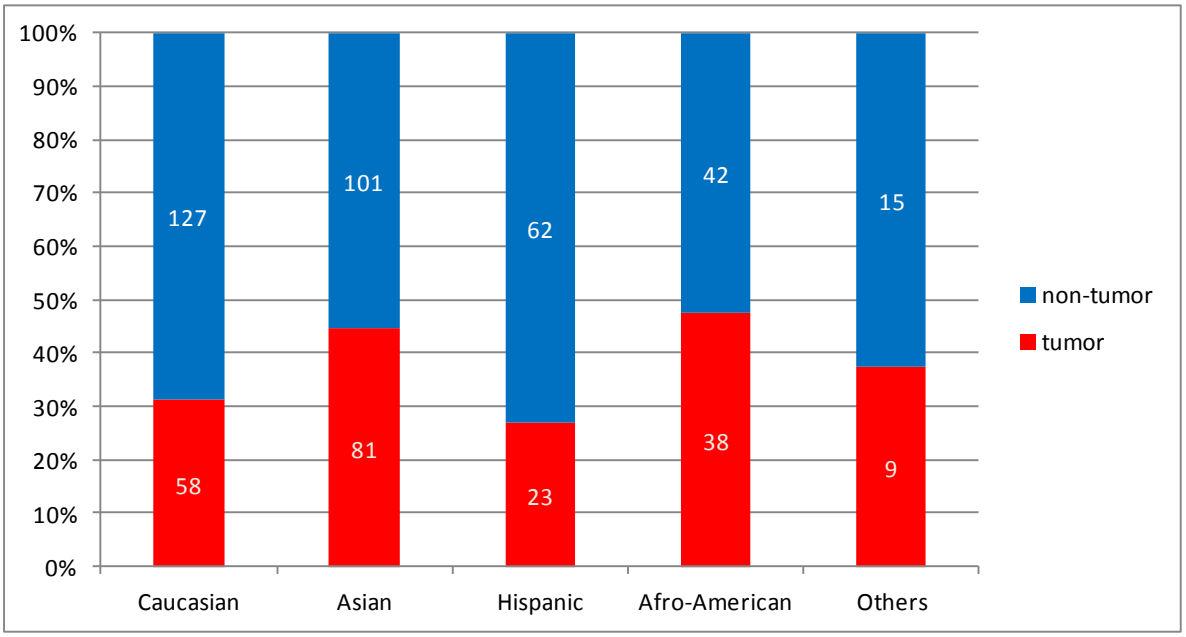
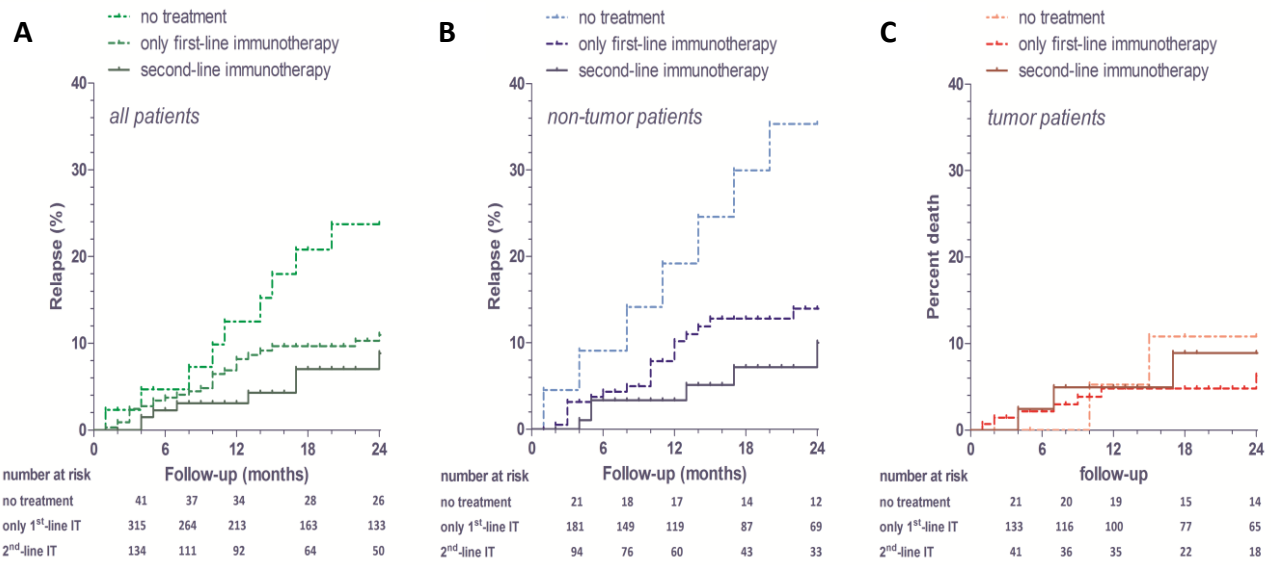
Figure S1: Frequency of tumor association according to ethnicity



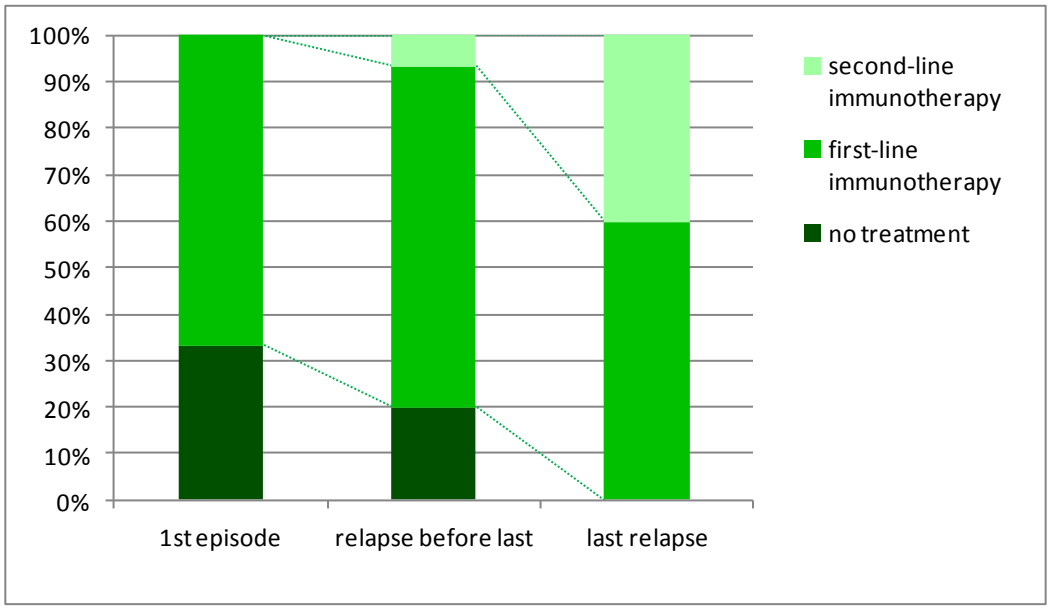
The frequency of a tumor was higher in African-Americans and Asians (p = 0·007). “Others” include 10 native American Indians and 14 native Pacific Islanders.

Figure S2: The frequency of relapses is affected by treatment only in patients without tumor



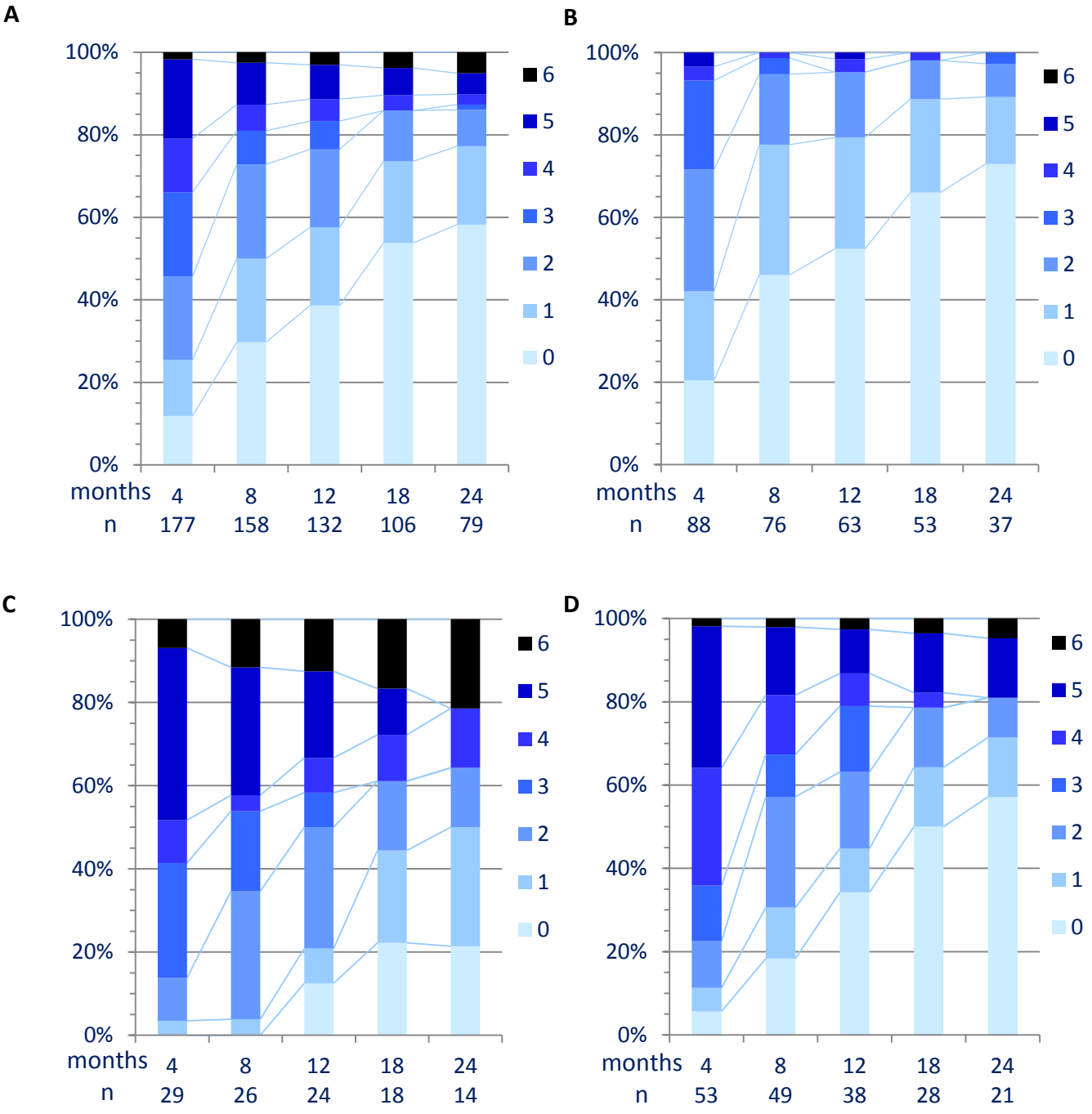
Panel A: All patients (p = 0·038)
Panel B: Patients without tumor (p = 0·007)
Panel C: Patients with tumor (p = 0·77)
Numbers of patients at risk are provided at 4, 8, 12, 18 and 24 months from onset.

Figure S3: Second-line immunotherapy in patients with multiple relapses reduced the risk of subsequent relapses



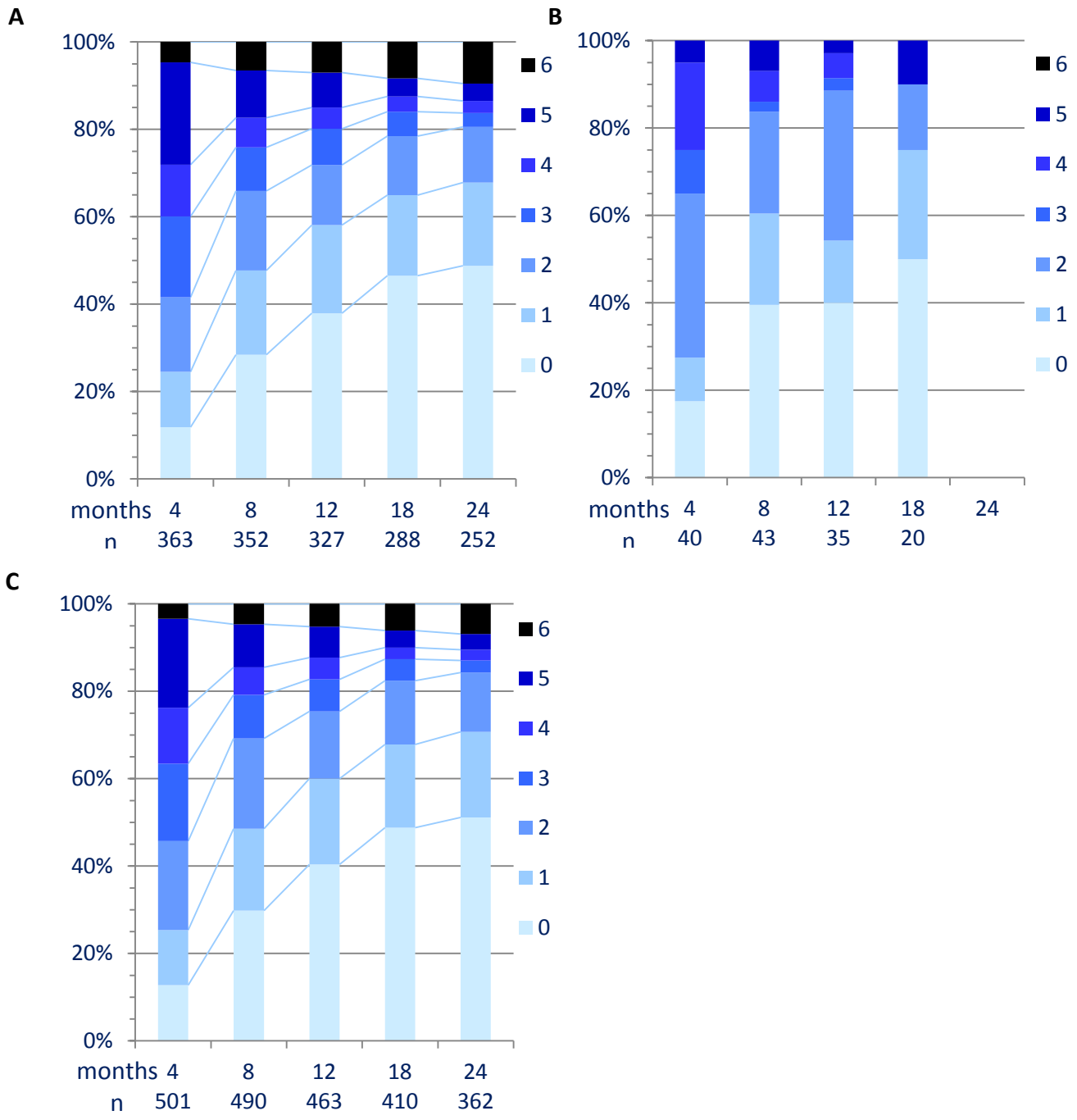
Fifteen patients had multiple relapses. The introduction of second-line immunotherapy to treat a relapse increased the likelihood that this relapse was the last (p = 0·024, Fisher-Freeman-Halton test).

Figure S4: Clinical outcome after extended follow-up in children



Panel A: All children
Panel B: Patients who responded to first-line immunotherapy (steroids, IVIg, plasmapheresis)
Panel C: Patients who failed first-line immunotherapy and did not receive second-line therapy
Panel D: Patients who failed first-line immunotherapy and received second-line therapy (rituximab, cyclophosphamide, or both)
Outcome was measured by modified Rankin scale (mRS).[1] Seven patients included in panel A did not have immunotherapy or tumor removal.

Figure S5: At last visit the mRS of patients who discontinued follow-up was better than that of patients who continued follow-up



Panel A: All patients with complete follow-up
Panel B: Patients who discontinued follow-up
Panel C: All patients with complete and imputated follow-up
Outcome was measured by modified Rankin scale (mRS).[1]

Table S1: List of countries and number of referrals

	number of patients
Argentina	1
Australia	6
Austria	1
Belgium	3
Brazil	6
Canada	28
Chile	4
China & Hong Kong	8
Colombia	2
Finland	2
France	10
Germany	12
Greece	1
India	6
Ireland	1
Israel	2
Italy	2
Japan	111
Mexico	6
Netherlands	4
New Zealand	10
Norway	1
Philippines	1
Portugal	1
Puerto Rico	4
Saudi Arabia	1
Singapore	2
South Corea	5
Spain	45
Sweden	3
Switzerland	6
Taiwan	15
Turkey	3
United Kingdom	2
United States	262

Table S2: Demographic features

(n = 577)		Non-tumor		Tumor		All		
Age at onset	(median, range; years)	18	(0·7 - 85)	25	(7 - 76)	21	(0·7 - 85)	< 0·0001 *
Gender	Female	255	71%	213	97%	468	81%	< 0·0001 #
	Male	102	29%	7	3%	109	19%	
Female	< 12	64	94%	4	6%	68		< 0·0001 ‡
	12-44	179	47%	205	53%	384		
	≥ 45	12	75%	4	25%	16		
Male	< 12	43	100%	0	0%	43		
	12-44	50	93%	4	7%	54		
	≥ 45	9	75%	3	25%	12		
Tumor diagnosis	Before			9	4%			
related to onset	Simultaneously			177	81%			
of encephalitis	After			33	15%			
	Unknown			1				
Prodromal symptoms	Yes	158	44%	140	64%	298	52%	< 0·0001 #
	No	199	56%	80	36%	279	48%	

*age at onset by Mann Whitney U test; # Fisher-Exact test; ‡ Tumor frequency in females <12 and >45 years versus 12-44 years.

Table S3: Brain MRI, EEG and CSF findings

(n = 577)		number	%	
MRI abnormalities	Yes	180	33%	
	No	360	67%	
	Unknown	37		
EEG	Abnormal	432	90%	
	Slow pattern *	398	83%	
	Epileptic features *	115	24%	
	No abnormalities	50	10%	
	Unknown	95		
CSF	Abnormal	418	79%	
	Pleocytosis *	402	76%	
	High protein *	93	17%	
	No abnormalities	114	21%	
	Unknown	45		
Sensitivity antibodies [#]	CSF	250	100%	< 0·0001
(250 random patients)	Serum	213	85%	

* The abnormalities of the EEG and CSF are given in grey; therefore, these percentages add up to over 100%.

[#] The sensitivity of serum and CSF NMDAR antibodies was determined by testing 250 paired serum and CSF samples (obtained on the same date) from patients selected using a random integer generator (http://www.random.org/integers/) among 415 patients from whom paired samples were available. A sample was considered positive if it fulfilled the following criteria: characteristic immunostaining of the neuropil of rat brain and specific reactivity with HEK cells expressing NR1 subunits of the NMDAR. While all CSF were positive in both techniques, 8% of sera did not react with brain and 14% did not react with HEK-NR1 cells.

Table S4: Clinical features of patients who died

Patient	Age	Gender	Tumor (found)	mRS before death	Time from symptom onset to death (weeks)	Cause of death	Anti-NMDAR encephalitis diagnosed before death
1	5	Female	No	5	3	Unknown	No
2	76	Male	Metastatic small-cell lung cancer (post-mortem)	5	3	Acute respiratory distress, probably due to atrial fibrillation and cardiac failure	No
3	38	Male	No	5	3	Stevens-Johnson syndrome secondary to phenytoin	Yes
4	18	Female	No	5	8	Sepsis, asystole	No
5	27	Female	No	5	8	Acute respiratory distress, renal failure	Yes
6	25	Female	OT (post-mortem)	5	8	Pulmonary embolism	Yes
7	24	Female	OT (post-mortem)	5	13	Stopped support	No
8	26	Female	OT (post-mortem)	5	13	Pulmonary embolism	No
9	85	Female	No	5	13	Respiratory failure	Yes
10	22	Female	No	5	13	Septic shock	Yes
11	12	Male	No	5	13	Septic shock	Yes
12	15	Female	No	5	13	Septic shock, multi-organ failure	Yes
13	20	Female	OT (simultaneously)	5	13	Complications of the ICU	Yes
14	65	Female	OT (before, but surgery only while NMDAR)	5	13	Multi-organ failure, peritoneal metastases	Yes
15	50	Female	No	5	17	Unknown	Yes
16	59	Male	No	5	17	Prolonged status epilepticus	Yes
17	35	Female	OT (simultaneously; not removed)	5	17	Cardiorespiratory failure	Yes
18	14	Female	OT (Simultaneously)	5	21	Encephalitis, unexpectedly	Yes
19	32	Female	OT (Simultaneously)	4	21	Severe hypothermia and cardiac arrest	Yes
20	27	Male	No	5	23	Sudden cardiac arrest	Yes
21	9	Female	No	5	26	Multi-organ failure	Yes
22	30	Male	TT (simultaneously)	3	26	Tumor infiltration of bone marrow, bleeding	Yes
23	20	Female	OT (simultaneously)	5	26	Autonomic failure, arrhythmia	Yes
24	25	Female	0	5	34	Sepsis	Yes
25	17	Female	0	5	39	Septic shock	Yes
26	34	Female	0	5	43	Arrhythmia	Yes
27	27	Female	OT (simultaneously)	5	60	Complications (disease-related) in nursing home	Yes
28	27	Female	OT (simultaneously)	5	65	Pneumonia	Yes
29	30	Female	OT (at relapse)	3	86	Pulmonary embolism	Yes
30	40	Female	OT (simultaneously)	5	108	Autonomic instability	Yes

mRS, modified Rankin Scale; OT, ovarian teratoma; TT, testicular tearoma

Table S5: Clinical features of relapses

		n	%
Patients		45	
Relapses		69	
number of relapses	1	30	67%
	2	9	20%
	3	4	9%
	4	1	2%
	5	1	2%
compared to first episode	Milder	46	67%
	Comparable	16	23%
	Worse	7	10%

		first episode		all relapses		p
mono-symptomatic	psychiatric only	0	0%	18	26%	< 0·0001 *
	neurological only	2	4%	6	9%	
	multisymptomatic	43	96%	45	65%	
maximum mRS	2	0	0%	5	4%	< 0·0001 #
	3	5	6%	27	20%	
	4	7	8%	22	16%	
	5	33	37%	15	11%	
ICU	Yes	29	64%	12	17%	< 0·0001 *
	No	16	36%	57	83%	

		first episode		second episode		P
tumor cases §	tumor removal	4	33%	8	67%	0·043 *
	no tumor removal	6	50%	2	17%	
	no tumor	2	17%	2	17%	

Fisher-Freeman-Halton test; * Fisher-Exact test;
§ Twelve patients with teratoma either at symptom presentation or thereafter had neurological relapses. At relapse, 8 patients had tumor removal including 2 with newly identified teratomas and 6 whose tumor was not removed during the initial episode. One of these 6 patients had a second relapse without tumor recurrence.
mRS = modified Rankin scale;[1] ICU = intensive care unit

Table S6: Treatment and outcome of relapses

		first episode		last relapse		p	
Outcome (best mRS) after first episode and last relapse [§]	0	18	40%	18	40%	1·00	*
	1	6	13%	11	24%		
	2	11	24%	6	13%		
	3	7	16%	4	9%		
	4	3	7%	4	9%		
	5	0	0%	1	2%		
	6	0	0%	1	2%		
Immunotherapy	None	9	20%	5	11%	0·19	#
	first-line	27	60%	23	51%		
	second-line	9	20%	16	36%		
	Unknown	0	0%	1	2%		
Immunotherapy (*non-tumor patients only*)	None	7	21%	0	0%	0·004	#
	first-line	20	61%	18	55%		
	second-line	6	18%	14	42%		
	Unknown	0	0%	1	3%		

* Fisher-Exact test mRS 0-2 vs. 3-6. # Fisher-Freeman-Halton test;
§ Six of 10 patients with poor outcome (mRS 3-6) after relapse, had severe residual symptoms from previous episodes of encephalitis; one of them suddenly died after recovering to the previous baseline status (mRS 3).
mRS = modified Rankin scale[1]

Table S7: Overview of treatments in children

(n=177)		Non-tumor		Tumor		All		Fisher Exact
N		142		35		177		
Time from symptom onset	(median, IQ range)	21	(21)	14	(14)	21	(21)	0·017 #
until treatment	(range, days)		(7-730)		(3-730)		(3-370)	
First-line immunotherapy		137	96%	31	89%	168	95%	0·077
	Steroids	129	91%	29	83%	158	89%	0·22
	IVIg	121	85%	26	74%	147	83%	0·14
	Plasmapheresis	34	24%	16	46%	50	28%	0·020
Second-line immunotherapy		48	34%	8	23%	56	32%	0·23
	Rituximab	37	26%	5	14%	42	24%	0·19
	Cyclophosphamide	22	15%	7	20%	29	16%	0·61
Other immunotherapy †		10	7%	1	3%	11	6%	0·70
Time from symptom onset	(median, IQ range)			1.0	(1·8)			
until tumor removal	(range, months)				(0·1 - 16·3)			
Surgery		3	2%	35	100%			< 0·0005
	during initial episode	3		30	86%			
	at relapse	0		1	3%			
	after recovery	0		4	11%			
Failure of first-line immunotherapy *	yes	70	49%	12	34%	82	46%	0·24
	no	67	47%	19	54%	86	49%	
	surgery, no immunotherapy	0	0%	2	6%	2	1%	
	no treatment	5	4%	2	6%	7	4%	

Mann/Whitney U test; † Azathioprine, mycophenolate mofetil, tacrolimus or methotrexate;
* Six non-tumor patients who had responded to first-line immunotherapy during the initial episode did not respond at relapse; one patient with teratoma who did not receive immunotherapy at initial episode did not respond to immunotherapy at relapse.

Table S8: Factors associated with good outcome (mRS 0-2) in children

A. Multivariable analysis

		p	OR	95% CI		events
ICU stay		0·004	0·15	0·06	0·39	140
time until treatment initiation (log_e)		0·067				
follow-up		< 0·0001				
	4 months *		0·03	0·01	0·10	80
	8 months *	< 0·0001	0·27	0·09	0·75	46
	12 months *	0·28	0·40	0·14	1·15	8
	18 months *	0·045	1·04	0·33	3·29	6
	24 months *	0·94	1·00			0
age (log_e)		0·048	1·77	1·05	2·98	140
maximum mRS		0·39				

B. Multivariable analysis first-line failure

		p	OR	95% CI		events
ICU stay		0·006	0·09	0·01	0·49	48
follow-up		< 0·0001				
	4 months *		0·01	0·00	0·06	15
	8 months *	< 0·0001	0·15	0·04	0·62	24
	12 months *	0·14	0·32	0·07	1·36	5
	18 months *	0·085	0·98	0·21	4·48	4
	24 months *	0·97	1·00			0
age (log_e)		0·19	1·70	0·77	3·75	48
second-line treatment		0·081	3·35	0·86	12·98	48

A: Multivariable analysis for all children.
B: Multivariable analysis for children who failed first-line immunotherapy.
*To assess continuous improvement over time, the outcome at each individual time point was compared with that of the previous time point, with the p values indicated as well as the amount of events in those specific months after the previous time point. After 8 months the number of patients achieving good outcome (or "events") becomes small (as reflected in the large confidence intervals). Patients improving from mRS 2 to 0 or 1 (or from 5 to 4 or 3) are not counted as events and therefore not visible in the table; these are all considered good outcome (or poor outcome) respectively). The 24 month follow-up is the reference value for the odds ratios (and the associated lower and higher range of the confidence interval) of individual time points.
OR = odds ratio; CI = confidence interval; log_e = natural logarithm; mRS = modified Rankin Scale; ICU = intensive care unit

References

1. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.