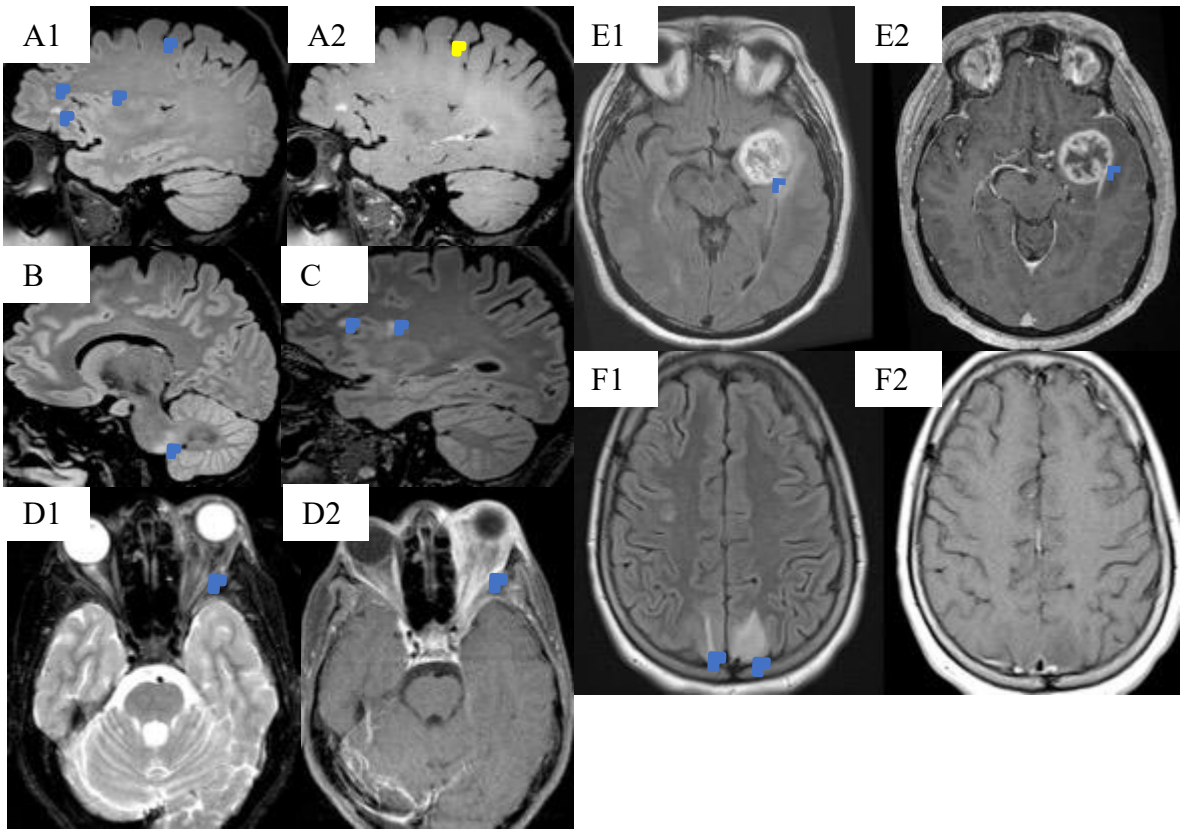
Patient	Family	Sex	Infiltrative lymphoctosis				Autoimmue cytopenia	Hypogammaglob uinemia	Other	Spinal fluid inflammation	Age at first clinical AI	Age at CNS AI diagnosis
			CNS	GI	Lung	Liver						
1	A	M	+	+	+		±	+	Pan hypo-pituitary	+	14	16
2	B	M	+	+	+		±	+	IDDM	+	22	30
3	C	F	±	+	±		+	+	Thyroid	+	11	11
4	D	M	+	+	+		+	+	**IDDM**	+	9	23
5	E	M	+	+	+		+	+	**IDDM**	+	3	15
6	F	M	+		+		±	+		+	9	14
7	G	M	+	+	+		±	+		+	9	34
8	G	F								+	n/a	30
9	H	M	+	+	+		±	+		+	6	9
10	I	M	+	+	+		±	+	Thyroid	+	2	17
11	J	M	+	+	+		±	±	Growth hormone deficiency	+	12	16
12	K	F	+	+	+		±	+			9	14
13	L	M	+		+	+	±	+		n/t	7	24
14	M	F	+	±	+		+	+		n/t	2	11
15	N	F	+	±	+		+	+		+	17	23
16	O	F		±			+	±		+	12	26

Supplemental Table 1. Demographics and clinical CTLA-4h disease reported in medical records of patients with objective evidence of neuroinflammation. Organs with infiltrative lymphocytosis were determined either by biopsy or, if biopsy was not performed, radiological evidence of inflammation. Autoimmune cytopenia included autoimmune hemolytic anemia, thrombocytopenia, lymphopenia, or any combination. Hypogammaglobulinemia was determined by the presence of a nadir of IgG <700 mg/dL. Other manifestations included presumed immune-mediated clinical disease or cancer. IDDM: insulin dependent diabetes mellitus type 1; thyroid: any autoimmune mediated thyroiditis; Pan hypopituitary: lab evidence of decreased pituitary hormone production; Bolded and underlined values represent the presenting clinical manifestation of disease. n/a: not applicable. n/t: not tested.

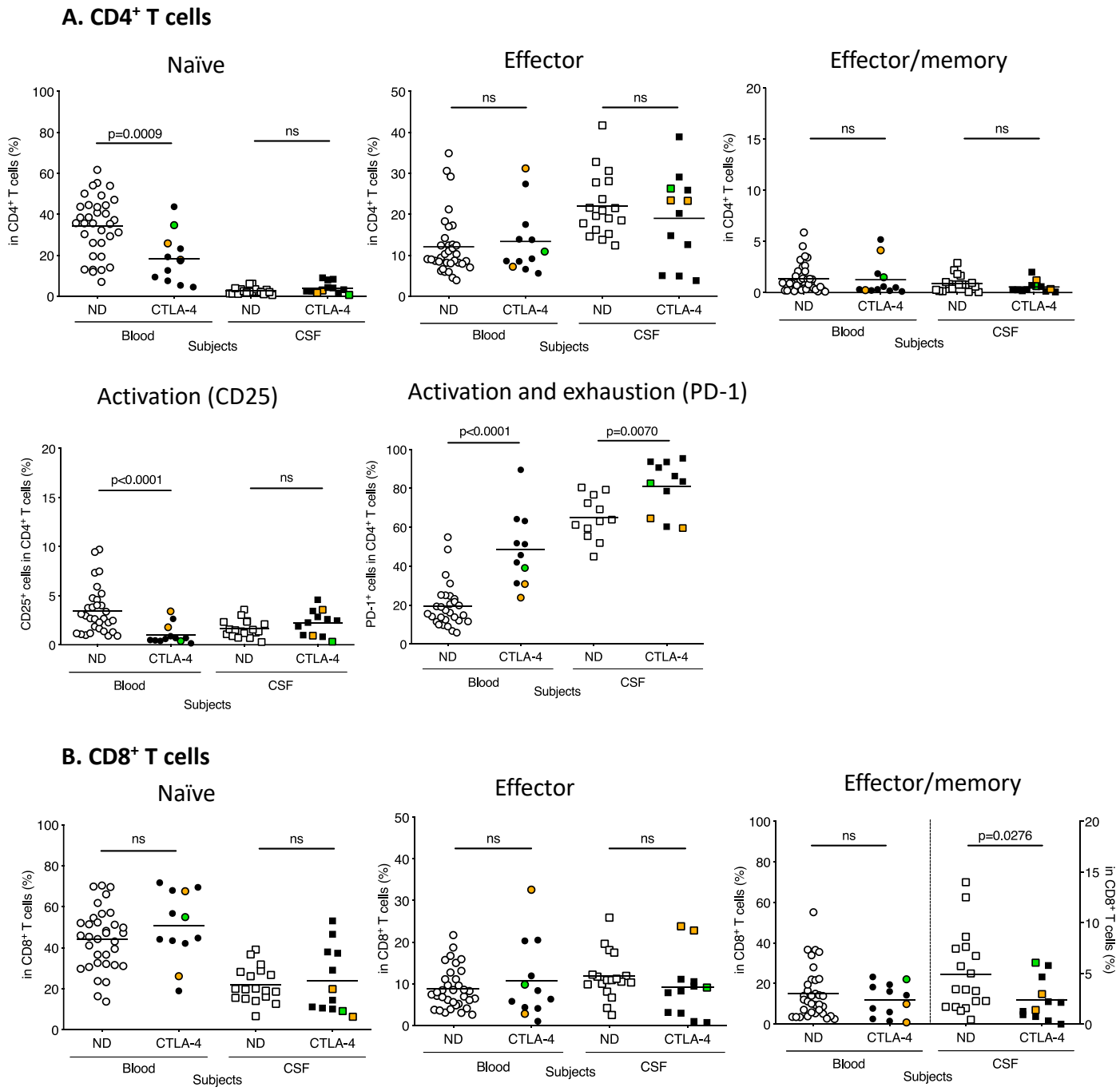
Group	Sample	Age	Gender	CSF cell concentration (cells/μl)
	Blood/CSF, n	Mean ± SD	Female n (%)	Mean ± SD
ND	31 / 18	47.26 ± 9.64	15 (48.39%)	1.25 ± 0.61
CTLA-4	12 / 12	23.92 ± 10.22	5 (41.67%)	18.93 ± 13.73

Supplemental Table 2. Demographics of the cohorts that underwent flow cytometric analysis. CSF: cerebrospinal fluid, SD: standard deviation, ND: normal donors.



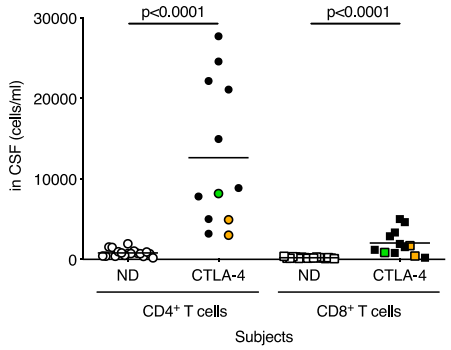
Supplemental Figure 1. Additional radiological findings in CTLA-4h. (A) 54 year-old female, first degree relative of patient 2, with CTLA-h and inflammatory disease causing hypogammaglobulinemia and inflammation of gastrointestinal and pulmonary tissues. Serial MRI over 3 years did not detect new or enhancing lesions on MRI. Neurological complaints included episodic migraines. T2-FLAIR (A1) and post-contrast T2-FLAIR (A2) with nonspecific hyperintense foci in the white matter (blue chevrons) and a focus of leptomeningeal enhancement (yellow chevron). (B) 30 year-old female, patient 8, without evidence of systemic CTLA4-h inflammatory disease, underwent imaging for facial numbness. She underwent LP to evaluate cause of headaches and was found to have OCB but no pleocytosis. T2-FLAIR image showing a lesion in the inferior portion of the pons, which was stable over 4 years of follow-up and never enhanced following contrast. No additional lesions developed. (C) 49 year-old male, first degree relative of patient 9. This patient reported migraine headaches as a teenager but had never previously been imaged until this screening MRI. T2-FLAIR image showing nonspecific foci in the subcortical white matter. The lesions have been stable in appearance over 2 years of follow-up. (D)15 year-old male, first degree relative of patient 1, with CTLA-4h and multi-organ inflammatory disease developed headache and proptosis. Fat-suppressed T2-weighted (D1) and T1-weighted (D2) images showing a large inflammatory infraorbital mass (chevron), confirmed on biopsy as an infiltrate of lymphocytes. (E) 72 year-old man, second degree relative of patients 7 and 8, without any known CTLA-4h associated disease developed headaches and memory loss. Post-contrast T2-FLAIR (E1) and T1-weighted (E2) images showing a large enhancing mass in the left temporal lobe (chevron). The biopsy showed a gliosarcoma. (F) 19 year-old man with CTLA-4h and severe cytopenias presented following a seizure following rituximab infusion. T2-

FLAIR (F1) and post-contrast T1-weighted (F2) images showing bilateral occipital lesions (chevrons) that were not contrast enhancing, consistent with posterior reversible encephalopathy syndrome (PRES).


A. CD4+ T cells
Naïve
Effector
Effector/memory
in CD4+ T cells (%)
p=0.0009
ns
ND
CTLA-4
Blood
CSF
Subjects
Activation (CD25)
Activation and exhaustion (PD-1)
CD25+ cells in CD4+ T cells (%)
PD-1+ cells in CD4+ T cells (%)
p<0.0001
p=0.0070
B. CD8+ T cells
in CD8+ T cells (%)
p=0.0276

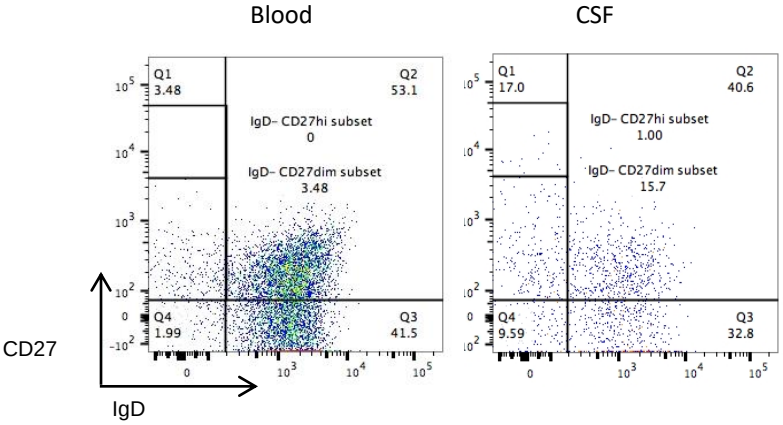
C. Absolute T Cells in CSF

Absolute $CD4^+$ and $CD8^+$ T cells in CSF

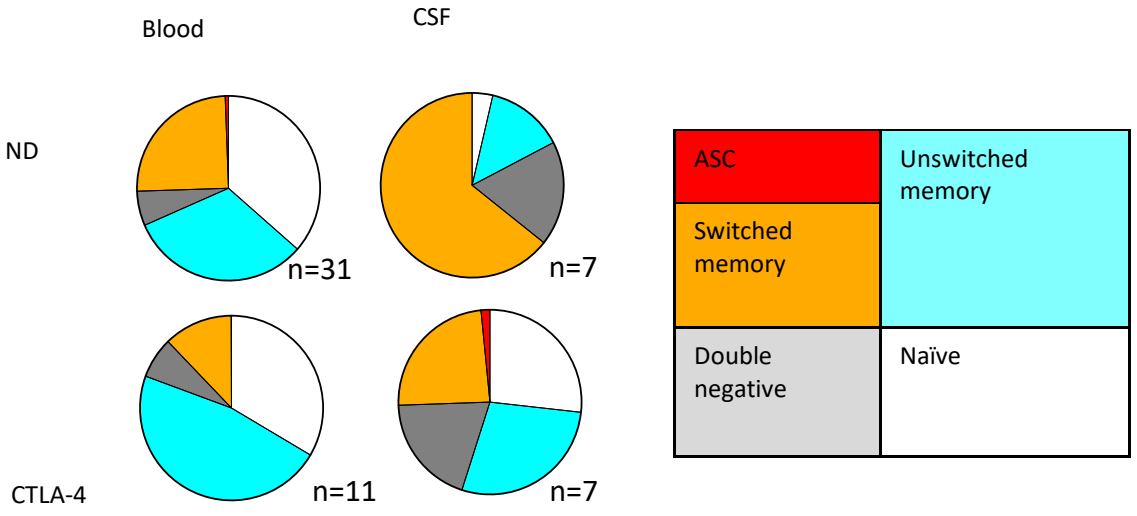


D. B Cells

Representative Flow



Proportion of B cell subtypes



Supplemental Figure 2. Additional flow cytometric data of cell populations from blood and cerebrospinal fluid (CSF) in cohorts of healthy normal donors (ND) and CTLA-4h patients with neuroinflammation. Within the CTLA-4h cohort, solid black data points represent patients with neuroinflammatory lesions seen on MRI coincident with CSF sampling, orange dots represent patients with evidence of inflammation in CSF only, and green dots a patient with neuroinflammatory lesions only on remote MRI scans. All values are presented as a percentage of cell subtype within the total population of cell type. Statistical testing was performed with the Mann-Whitney test and significance was set at $p < 0.05$. (A) $CD4^+$ and (B) $CD8^+$ T-cell subtypes, including naïve ($CD45RA^+CD27^+$), effector ($CD45RA^+CD27^-$), effector/memory ($CD45RA^-CD27^-$), activated (CD25), and activated/exhausted (PD1). (C) Absolute $CD4^+$ and $CD8^+$ T-cell counts in the CSF. (D) Representative flow cytometry plots of B-cells from blood and CSF form a patient with CTLA-4h. Proportion of different B-cell subtypes within blood and CSF of ND and patients with CTLA-4h.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.