



# Neurological Involvement in Childhood Evans Syndrome

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## Abstract

**Purpose** Immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) are associated in the definition of Evans syndrome (ES). The occurrence of neurological involvement in this population is poorly described and suggests an underlying primary immunodeficiency (PID). We aimed to describe the clinical manifestations, evolution, and PID profiles of these patients.

**Methods** OBS’CEREVANCE is a French, nationwide prospective cohort that includes children with chronic ITP, AIHA, and ES. Patients with a neurological involvement were described. Centralized radiological and pathological reviews and genetic analyses were performed.

**Results** On October 2016, eight patients (7/181 ES, 1/371 AIHA, and 0/615 ITP) were identified, all male, with a median age (range) at cytopenia onset of 11.5 years (1.6–15.8). Neurological symptoms appeared with a median delay of 6 years (2.5–18) after cytopenia and were polymorphic: seizures ( $n = 4$ ), cranial nerve palsy ( $n = 2$ ), Brown-Sequard syndrome ( $n = 2$ ), intracranial pressure ( $n = 2$ ), vertigo ( $n = 1$ ), and/or sensory neuropathy ( $n = 1$ ). Magnetic resonance imaging (MRI) showed inflammatory lesions, confirmed by pathology for five patients with macrophagic or lymphoplasmocytic infiltrates. All patients had other relevant immunopathological manifestations: pulmonary nodules ( $n = 6$ ), lymphoproliferation ( $n = 4$ ), abnormal immunophenotype ( $n = 8$ ), and hypogammaglobulinemia ( $n = 7$ ). Treatment consisted of steroids that improved symptomatology and MRI. Five patients relapsed and three had an asymptomatic radiological progression. A PID was identified in 3/8 patients: 22q11.2 microdeletion ( $n = 1$ ) and CTLA deficiency ( $n = 2$ ).

**Conclusion** Neurological involvement is a rare and severe late event in the course of childhood ES, which can reveal an underlying PID. Imaging and pathology examination highlight a causative immune dysregulation that may guide targeted therapeutic strategies.

**Keywords** Autoimmune cytopenia · Evans syndrome · primary immunodeficiency · CTLA deficiency · neurological disorder · lymphoproliferation

## Introduction

Evans syndrome (ES) is defined by the association between immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA). These autoimmune cytopenias

(AIC) are relatively rare during childhood [1, 2]. In France, 10 new cases of ES per year are estimated to be diagnosed in children, 30–50 of AIHA and 500–800 of chronic ITP [3, 4]. In an unknown number of cases, AIC can be secondary to an underlying primary immunodeficiency (PID). Classically, the PID that seemed to frequently underlie AIC involved autoimmune lymphoproliferative syndrome, common variable immunodeficiency and Wiskott-Aldrich syndrome [5–10]. In recent years, alterations of several genes causing PID have been identified in patients with hematological autoimmunity as one of the main manifestations, often preceding other symptoms by years [11–13]. An increasing number of patients with cytotoxic T-lymphocyte-associated protein 4 (CTLA4)/

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lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency, STAT3 gain-of-function mutations or activated PI3K-delta Syndrome are being described, broadening the spectrum of identified PID [14, 15]. Consequently, within the childhood AIC population, non-hematological manifestations may be related to a dysimmune process caused by an underlying PID. Their identification is crucial to classifying the disease and for proposing optimal treatment with an adequate follow-up, as well as for improving knowledge about those rare conditions. The characteristics of neurological involvement in these patients are poorly understood. We sought to identify patients with these neurological manifestations among the French cohort of childhood AIC, to describe the clinical radiological and pathological features and their outcomes, and to search for a PID genetic etiology.

## Methods

### Patient Selection

The OBS'CEREVANCE is a nationwide prospective observational cohort (based at the University Hospital of Bordeaux), which includes all consecutive French patients aged less than 18 years presenting with AIHA, chronic ITP, or ES since 2004, as described previously [3, 16]. Written informed consent had been obtained from parents and, when old enough, the patients. The database was declared to the French Commission for Information Technology and Civil Liberties (November 9, 2009; 1396823V0).

### Inclusion Criteria

Patients presenting any reported neurological manifestations were first screened through the database in October 2016. Medical records were individually analyzed to confirm or deny their inclusion in the study. Inclusion criteria were any neurological manifestations excluding isolated febrile seizures, symptomatology due to an intracranial hemorrhage or traumatism, and isolated developmental delay.

### Data Collection

Clinical and biological data were collected from the original center in charge of the patient. Data collection ceased on April 30, 2017. Autoimmune neutropenia (AIN), the severity and the evolution of AIC, used the pre-established definitions [3, 17]. Lymphocyte phenotype was considered in the absence of concomitant or recent immunosuppressive drugs and immunoglobulin test before rituximab or 2 years after the last injection.

## Centralized Radiological and Pathology Review

A centralized review of neurological magnetic resonance imaging (MRI) at the onset and during the follow-up was performed by HDLP (Trousseau Hospital, Paris).

Tissue samples of patients who underwent a cerebral biopsy were collected for centralized pathology review by PV (Saint-Anne Hospital, Paris).

## Molecular Biology Analysis

A blood sample was collected from the patient. Constitutional DNA was extracted for gene sequencing (FRL, Imagine Institute, Paris). Initially, a candidate gene approach based on the patient phenotype with successive Sanger's method was used. Implementation of panel-based next-generation sequencing (NGS) in 2017 allowed simultaneous analysis of 250 PID genes. This homemade panel (designed by FRL and BN) has been made to contain known genes or ones suspected to be associated with immunopathological manifestations, regardless of the organ involved. Depending on the gene and based on the literature search, the panel encompassed the entire gene sequence, exons, or mutational hotspots. NGS DNA gene panel sequencing was performed using Illumina sequencing technology (San Diego, California). A depth of coverage of > 100 reads was required to determine a variant. A variant was considered to be pathogenic if its pathogenicity had already been described. If pathogenicity had not been described, it was assessed through a review of public databases (ClinVar and Human genome variation database) and in silico analysis (PolyPhen6 or the Sorting Intolerant From Tolerant algorithm). Surface staining of the corresponding protein (CTLA4) was used to support NGS findings. Variants not deemed pathogenic were excluded.

## Statistical Analysis

Epidemiological and clinical characteristics of the patients with a neurological involvement were compared to the whole cohort. Categorical data were compared using Fisher's exact test and continuous data were compared using non-parametric Wilcoxon test. All tests were two-sided with a statistical significance threshold of  $p < 0.005$ ;  $p$  values between  $< 0.05$  and  $< 0.005$  were considered statistically suggestive [18].

## Results

### Population

Among the 1167 patients (615 ITP, 371 AIHA, and 181 ES) included in the OBS'CEREVANCE cohort at the time of the

selection, 8 patients fulfilled the inclusion criteria and all were male. A diagnosis of PID was known in one (incomplete DiGeorge syndrome). They were managed in seven different centers. The median follow-up since AIC onset was 12 years (range 6–26.5).

### Autoimmune Cytopenia

Of the eight patients, seven had an ES. Patient 3 had an isolated AIHA (Fig. 1). The median age at the first AIC onset was 10.5 years (1.6–15.8, Table 1). The patients with ES demonstrated a median delay between the two with AIC of 1.5 years (0–10.4), and five developed AIN after a median delay of 3.1 years (1–6.9) after first AIC onset.

All patients received several courses of steroids and all but one intravenous immunoglobulin (IVIg) to manage AIC. Second-line immunosuppressive therapies were used in seven children with a median of two (0–5) drugs per patient. The most commonly used was rituximab ( $n = 7$ ). A splenectomy was carried out in two of the patients.

At the last endpoint, all patients were in complete remission of the AIHA and 6/7 in complete remission of the ITP (the last was in partial remission). Nevertheless, only 1/8 had been

weaned off of all immunosuppressive medication for more than 12 months.

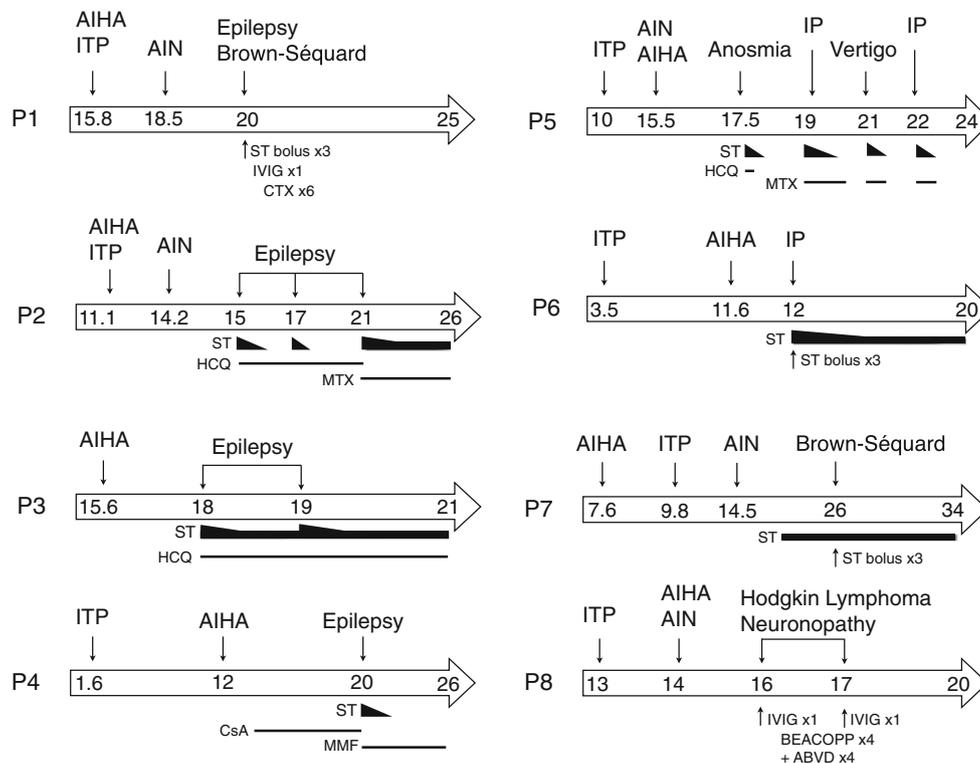
### Epidemiological Analysis

Distribution of cytopenia was different among the eight patients, as compared to the rest of the cohort, with a significantly higher proportion of ES (7/8 vs 174/1159,  $p < 0.0001$ ). The sex ratio of these seven ES patients compared to the 174 others was skewed toward a male predominance (7:0 vs 99:75,  $p = 0.04$ ). No other characteristics were found to be statistically different.

### Neurological Involvement Characteristics

#### Polymorphic Clinical Presentation

The neurological manifestations were observed after AIC onset (median 6 years (2.5–18, Fig. 1)). The median age at the appearance of the first symptoms was 17 years (12–26) and three patients developed several (2 to 4) manifestations (Table 2). Within a few days, symptoms had developed for each patient.



**Fig. 1** Clinical courses of the patients. Individual representation of the manifestations' clinical sequence. Age at the onset (years) is specified for each manifestation. Time scale is not representative. Each treatment used for the neurological involvement is represented below. ITP = immune thrombocytopenic purpura. ST = steroids therapy. IVIG = intravenous immunoglobulins. CTX = cyclophosphamide. HCQ =

hydroxychloroquine. IP = intracranial pressure. MTX = methotrexate. CsA = cyclosporine. MMF = mycophenolate mofetil. BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (1.33 mg/kg/day for 14 days). ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine

**Table 1** Description of AIC and genetic analyses

Patient	Cytopenia sequence	Age at diagnosis (years)				Severity at diagnosis		Treatments				Evolution		Genetic alteration
		First AIC	Second AIC	AIN	DAT	AIHA	ITP	CS	IV Ig	IS (nb)	SPX	AIHA	ITP	
1	Simultaneous ES	15.8		18.5	IgG	1	0	Yes	Yes	2	No	CR	PR	22q11.2 microdeletion*
2	Simultaneous ES	11.1		14.2	IgG	N/A	N/A	Yes	No	0	No	CR	CR	Heterozygous CTLA4 mutation c.316A>C; p.T106P
3	AIHA	15.6	N/A	N/A	IgG + C3	2	N/A	Yes	Yes	1	No	CR	N/A	Heterozygous CTLA4 mutation c.403dupA; p.Y135fsX
4	ITP then AIHA	1.6	12	N/A	IgG	1	2	Yes	Yes	5	No	CR	CR	No pathogenic mutation identified in the panel of 250 genes
5	ITP then AIHA	10	15.7	15.5	IgG + C3	2	2	Yes	Yes	2	Yes	CR	CR	No pathogenic mutation in RAG1 and RAG2
6	ITP then AIHA	3.5	12.4	N/A	IgG	N/A	N/A	Yes	Yes	2	No	CCR	CCR	No pathogenic mutation identified in the panel of 250 genes
7	AIHA then ITP	7.6	9.8	14.5	IgG + C3	2	2	Yes	Yes	4	No	CR	PR	No pathogenic mutation identified in the panel of 250 genes
8	ITP then AIHA	13	14	14	IgG	1	3	Yes	Yes	3	Yes	CR	CR	No pathogenic mutation identified in the panel of 250 genes

Severe ITP and AIHA conditions were defined as Buchanan score  $\geq 3$  and AIHA CEREVANCE score  $\geq 2$ , respectively, as described in Buchanan et al. J. Pediatr. 2002 and Aladjidi et al. Front. Pediatr. 2015, respectively

AIC autoimmune cytopenia, AIHA autoimmune anemia, ITP immune thrombocytopenia, ES Evans syndrome, AIN autoimmune neutropenia, DAT direct antiglobulin test, CS corticosteroids, IV Ig intravenous immunoglobulin, IS immunosuppressive therapy, SPX splenectomy, CR complete remission, PR partial remission, NR no remission, CCR continuous complete remission, N/A not applicable, nb number

Four patients presented seizures (temporal ( $n=2$ ), absence ( $n=1$ ), and/or generalized tonic-clonic episodes ( $n=4$ )); no one developed status epilepticus. Two patients presented with cranial nerve palsy, two had medullary symptomatology with Brown-Sequard syndrome, two patients had intracranial pressure, and one had peripheral vertigo. Patient 8 developed a sensory neuropathy with facial involvement unveiling a stage IVBb EBV-negative Hodgkin lymphoma diagnosis (with bone, hepatosplenic, and intracranial involvement). Except for this last case, neurological manifestations were isolated and not coupled to a hematological or immunopathological manifestation.

### Initial Radiological Evaluation: Multiple White Matter Localizations

Initial MRI identified unique ( $n=2$ ) or multiple ( $n=6$ ) lesions (Fig. 2). Six patients had supratentorial lesions involving the white matter. The localization was frontal ( $n=3$ ), parietal ( $n=2$ ), temporal ( $n=2$ ), and/or occipital ( $n=1$ ). Perilesional edema was present in four cases and

was responsible for a median line deviation in two cases. Three patients had subtentorial lesions involving the white matter of the cerebellum and causing an important perilesional edema, amygdala engagement, and/or ventricular dilatation. These lesions were associated with supratentorial localization in each case. Two patients had medullar lesions, two had a peripheral lesion, and two had a meningeal involvement.

The signal characteristics of all the lesions were similar with T2-hyperintense and T1-iso/hypointense pattern. At least one gadolinium-enhanced lesion was present in seven patients suggesting active injuries. Three patients presented a perivascular topography of the lesions.

### Lymphocytic Pleocytosis Was Concomitant in Some Patients

A cerebrospinal fluid (CSF) analysis was conducted for all patients (Table S1). Four had a CSF lymphocytic pleocytosis (median white cells 46/ $\mu$ L (18–102)). One

**Table 2** Neurological involvement and evolution

Patient	Clinical symptoms	Imagery	Evolution and last follow-up	Follow-up (years)
1	Generalized tonic–clonic seizure and right Brown–Séquard syndrome	Lesion of the whole spinal cord with T3–T5 gado + lesion associated to T4 spondylitis. Five supratentorial micronodular lesions (gado+)	Transient amelioration after ST (bolus) and IVIG. Improvement after 6 cyclophosphamide cycles. Persistence of incomplete spastic paraplegia with chronic urinary retention. Treatment by baclofen, dantrolene and surgery	5
2	(1) Absence seizures (2) Generalized tonic–clonic seizures (3) Generalized tonic–clonic seizures	(1) Posterior fossa nodular lesions (gado+) (2) Multiple supra- and subtentorial lesions (3) Right cerebellum lesion with meningeal involvement (gado+)	Three manifestations treated successfully by ST (daily). No more recurrence under lacosamide, levetiracetam, prednisone and methotrexate	10.5
3	(1) Temporal and generalized tonic–clonic seizure (2) Generalized tonic–clonic seizures	(1) Bilateral temporal lesions (gado+) (2) Left parietal lesion (gado+)	Two manifestations successfully treated by ST (daily). No more recurrence under lacosamide, levetiracetam, prednisone, hydroxychloroquine	3
4	Temporal and generalized tonic–clonic seizures	Bilateral temporal lesions (gado-)	ST (daily) for 5 months, switch from cyclosporine to mycophenolate mofetil, stable lesion. Three seizure recurrences under levetiracetam	6
5	(1) Anosmia, right oculomotor nerve palsy (2) Intracranial hypertension (3) Rotatory vertigo (4) Intracranial hypertension	(1) Right infiltrative frontoethmoidal lesion (gado+) with pachymeningitis (2) Left cerebellar lesion (gado+) (3) Left auditory canal lesion (gado+) (4) Right cerebellar lesion (gado+)	Four episodes treated successfully with ST (daily) ± methotrexate ± hydroxychloroquine. Persistence of nystagmus. Loss to follow-up	6.5
6	Left VI and VII cranial nerve palsy associated with intracranial hypertension	Posterior fossa tissue lesion (gado+). Right periventricular lesion (gado-)	Clinical improvement after ST (bolus + daily). Persisting sequels of facial palsy. Eight new asymptomatic supratentorial lesions (gado±) appeared during follow-up; regression under ST dose increase (daily)	5
7	Incomplete left Brown–Séquard + homolateral Horner’s syndrome	Left cervical spinal cord lesion (C5 to T2) (heterogeneous gado+). Whole spinal cord swelling	Clinical amelioration under ST (bolus). Persistence of sequelae (dysesthesia, partial motor deficit, dysuria) requiring therapy with duloxetine, clonazepam, pregabalin, and tramadol	8
8	Sensory ganglionopathy (cranial nerves III, IV, V, and VI palsy with four extremities-limb sensory troubles problems and proprioceptive ataxia)	Bilateral gadolinium-enhancement of intracranial portion of cranial nerves V. Vertebral lesions related to HL	Delayed amelioration following IV IG and chemotherapy Relapse, progressive amelioration with IV Ig. Persistent sensory disorders of all four limbs, occasional treatment with clonazepam	4

*Gado+* gadolinium enhancement, *Gado-* no gadolinium enhancement, *Gado±* gadolinium enhancement of some of the lesions, *ST* Steroid treatment, *CSF* cerebrospinal fluid, *HL* Hodgkin lymphoma, *N/A* not applicable

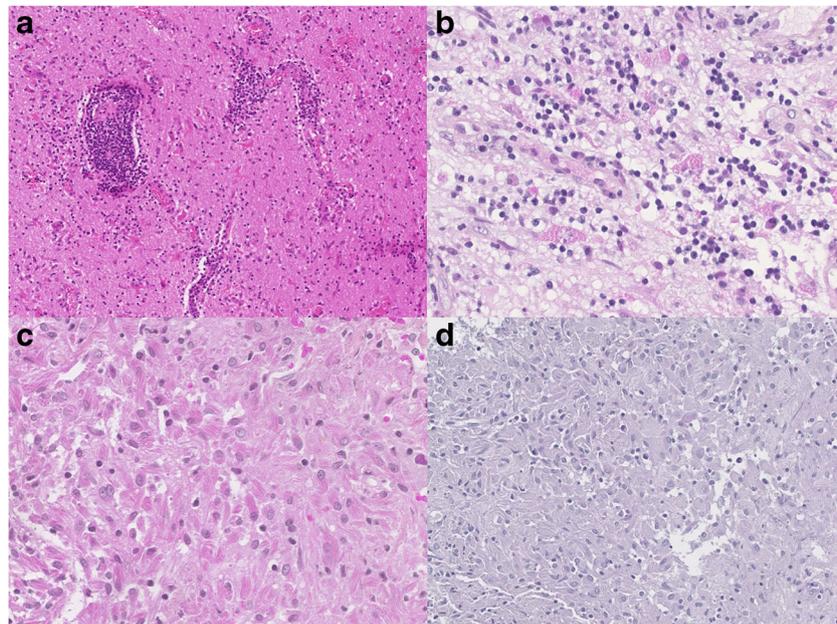
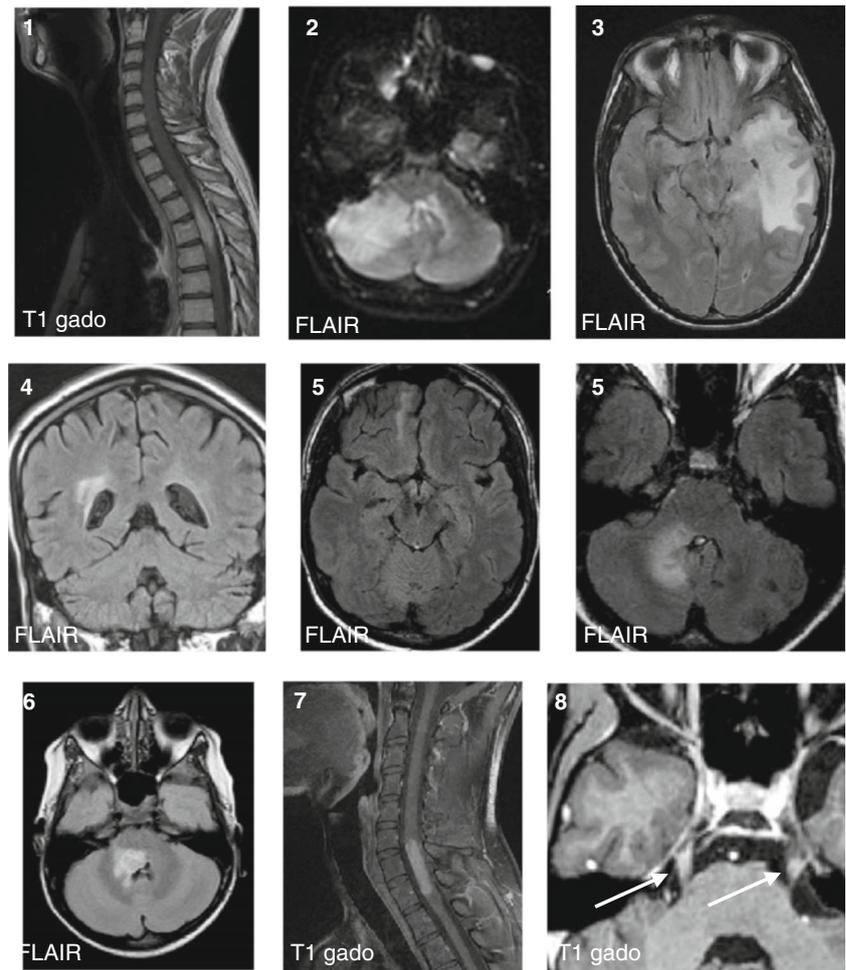
patient had an intrathecal immunoglobulin production. Anti-neuronal antibodies were tested for and returned a negative result for three patients. A lymphocytic phenotype in the CSF was evident for three patients, showing a CD3+ T cell predominance. The sensory neuropathy of patient 8 was associated with albumin-cytological dissociation in CSF and electromyography parameters showing demyelinating injury. Interictal electroencephalography of patients who presented seizures did not evidence focal abnormalities. No infectious agent was identified in any blood or CSF samples.

**Pathology-Revealed Inflammatory Process**

Five patients had a total of four cerebral, three cerebellar, and one spinal surgical biopsies (Table S2). A centralized review was performed for the samples of three patients (Fig. 3).

All patients presented an inflammatory infiltrate, which had a predominance of macrophages/histiocytes (*n* = 3) or T lymphocytes/plasmocytes (*n* = 5). In five cases, the infiltrate had a perivascular predominance or a characterized vasculitis, and in four cases, a

**Fig. 2** Representative neurological MRI of patients. Individual MRI at the manifestation onset (two distinct manifestations for patient 5). Each patient's ID is the upper number and the MRI sequence is the lower statement (T1 gado: T1-weighted sequence post gadolinium injection, FLAIR: T2-weighted sequence fluid-attenuated inversion recovery). For patient 8, the arrows show gadolinium-enhancement of both intracranial portions of cranial nerve V



**Fig. 3** Representative histological samples. **a** The three patients reviewed presented pleomorphic pseudo-tumoral masses, which were monolymphocytic and plasmocytic, with vasculitis and without necrosis (patient 5,  $\times 100$ ). **b** The inflammatory reaction contained numerous and

dispersed microgranular macrophages in poorly defined clusters (patient 2,  $\times 300$ ). **c** Some macrophages presented a striated aspect (patient 6,  $\times 300$ ). **d** Periodic Acid–Schiff reaction was negative on these macrophages (patient 6,  $\times 200$ )

granulomatous reaction was observed. A unique macrophage morphology was observed in four samples. No pathogen was found in any sample, nor any indirect sign of infectious process.

### Treatment Was Based on Steroids

Steroid treatment was used as first-line therapy for seven patients (Fig. 1). Five patients received daily intake (initial dose 1–2 mg/kg/day then progressive tapering) and three bolus steroids. Four patients received at least one other simultaneous therapy associated with steroids: hydroxychloroquine ( $n = 3$ ), methotrexate ( $n = 2$ ), IVIG ( $n = 2$ ), and mycophenolate mofetil ( $n = 2$ ).

Steroids allowed an initial clinical and radiological improvement for all cases except patient 1 (who received only bolus steroids) for whom a second-line treatment with cyclophosphamide was needed. All patients with seizures required a second-line of anti-epileptic treatment to control the recurrence of convulsions.

Patient 8 was treated with IVIG promptly, followed by the chemotherapy for Hodgkin's lymphoma. The neuropathy relapsed 10 months later. New IVIG courses allowed a progressive amelioration.

For three patients, new neurological manifestations appeared during the steroid tapering ( $n = 1$ ) or after the treatment was stopped ( $n = 2$ ). They were sensitive to a new high-dose steroid treatment. Three other patients developed new asymptomatic radiological lesions during the steroid tapering, which were identified on follow-up MRI. Increasing the steroid dose led to these lesions reducing in size.

At the last follow-up (median since the first neurological event = 5 years (3–10.5)), only two out of five patients could discontinue the daily steroids (at 5 and 30 months of the onset); the remaining three had pursued a continuous treatment for 2, 5, and 5 years. In two out of five patients, the nonsteroidal immunosuppressive drugs were stopped.

### Persistent Sequelae during the Follow-Up

At the last endpoint, epilepsy was controlled for four patients (total number of seizures  $\leq 5$  per patient) using anti-comitial therapy. All five patients who presented non-comitial manifestations displayed clinical sequelae, either minor ( $n = 2$ ), moderate ( $n = 1$ ), or severe ( $n = 2$ , requiring persistent symptomatic treatment).

In all patients, radiological lesions had decreased in size. Nevertheless, at the last radiological assessment, seven patients displayed persistent and stable radiological lesions (median follow-up MRI reviewed: four per patient (2–12), Fig. S1).

## Immunopathological Findings

### Non-neurological Immunopathological Manifestations Associated with AIC Were Present in all Patients

All patients developed at least one non-neurological immunopathological manifestation (Fig. 4). These manifestations appear a median of 8.5 years (0–15) after AIC onset and before or at the same time as neurological manifestations.

The most frequent ( $n = 6$ ) was chronic pulmonary nodules without any proven infection evoking granulomatous-lymphocytic interstitial lung disease (Table S3) [19]. In patient two, pulmonary involvement was a part of a multivisceral granulomatous disease with renal and digestive injuries.

Four patients had non-malignant lymphoproliferation, either superficial ( $n = 3$ ) or profound ( $n = 3$ ). The HL presented by patient 8 had a persistent complete remission at the 30 month follow-up. Four patients presented mucosal or cutaneous injuries, including eczema ( $n = 3$ ) and recurrent diarrhea without an identified etiology evoking immunopathological enteropathy ( $n = 2$ ). Opportunistic or unusual infections were rare. Patient 1 experienced severe chickenpox and patient 5 had streptococcus pneumonia meningitis.

### All Patients Presented Low Immunoglobulin Levels and/or Lymphocyte Count

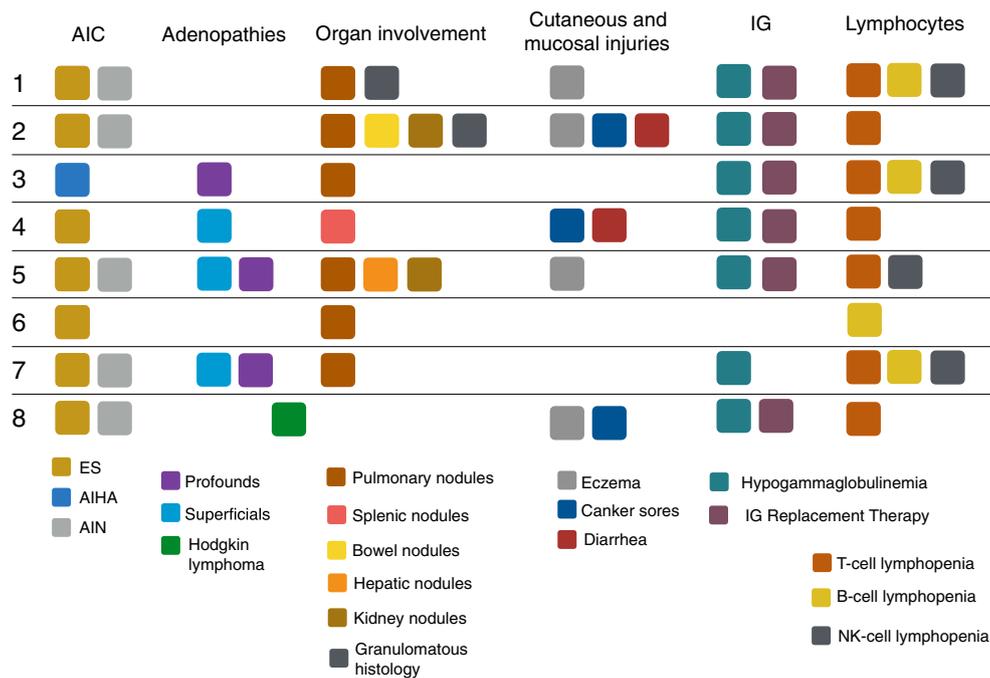
All but one patient presented hypogammaglobulinemia for their age (median IgG = 4.5 g/L (2.7–6)) associated with IgA ( $n = 5$ ) and/or IgM ( $n = 3$ ) deficiency (Table S4). Six received immunoglobulin replacement therapy before the onset of neurological involvement. All patients presented an abnormal lymphocyte phenotype with CD4+ T cells ( $n = 5$ ), CD8+ T-cells ( $n = 6$ ), B cells ( $n = 3$ ), and/or NK-cells ( $n = 1$ ) deficiency.

### Molecular Biology

Genetic analysis was performed on all patients and a PID was identified in three of them (Table 1). Patient 1 had a DiGeorge syndrome due to a 22q11.2 microdeletion. Two patients presented heterozygous mutations in the *CTLA4* gene, located within the exon 2. Both had not been previously described and predicted as pathogenic. Surface staining confirmed the diminution of protein expression. NGS could not have been performed for patient 5 (no follow-up).

## Discussion

Based on this large cohort for AIC appearing in childhood, we demonstrated that neurological manifestations represented a rare occurrence, appearing almost exclusively during the



**Fig. 4** Non-neurological characteristics of the patients. Individual summaries of the autoimmune cytopenia, non-neurological manifestations and immunological features of the patients. The complete descriptions are available in Table 1 (description of AIC and

genetic analyses), Table S3 (non-neurological organ involvement) and Table S4 (immunobiology). AIC = autoimmune cytopenia. ES = Evans syndrome. AIHA = autoimmune hemolytic anemia. AIN = autoimmune neutropenia. IG = immunoglobulins

course of ES. The clinical presentation was severe, heterogeneous, and caused by a dysimmune process. Despite their initial sensitivity to steroids, all patients presented a chronic evolution and some developed new lesions (symptomatic or not) at the treatment tapering. All of the patients presented miscellaneous immunopathological manifestations and PID was identified in three, including two *CTLA4* mutations.

Literature has rarely reported patients developing neurological manifestations associated with AIC and all but one in adulthood. One case (28 years old) described a lymphoplasmocytic lesion of the encephala before the onset of an ES [20]. Two cases (29 and 53 years) described demyelinating injuries after treatment for ITP (rituximab and splenectomy) [21, 22]. One patient (44 years) reported with ITP has developed myelitis attributed to a helicobacter infection [23]. Three patients (from a child of unspecified age to 50 years) with ES-developed polyradiculoneuropathy (chronic,  $n = 2$  or acute,  $n = 1$ ) [24–26]. This scarcity of data is consistent with the low number of patients identified within the OBS'CEREVANCE cohort.

The clinical presentations were acute and polymorphic, related to the lesion topography, which mainly involved the CNS. The MRI morphologies were similar and suggestive of an inflammatory process with an active lesion identified in all but one patient. In this last case (patient 4), the seizure was probably caused by a scar of an unidentified ancient lesion. The dysimmune process was confirmed by the initial work-up and two kinds of immune infiltrates were described by the pathology

examination, with either a predominance of lymphoplasmocytic (with T cells) or macrophagic/histiocytic cells. Interestingly, a very atypical and non-classified macrophage morphology was observed in four of the patients. Granulomas were identified in three patients, which is unusual in AIC [27].

Steroids were the main treatment, used alone or in association, and mostly with a daily intake scheme. The acute and sometimes severe presentation led to injection in the form of a bolus in some patients. This option may represent a good way to be rapidly effective. However, continuous immunosuppression seems necessary in the initial phase (in addition to bolus or alone) because the regrowth of the lesion is seen in some cases as steroid treatment ends or due to tapering. To this end, continuous steroids were effective in our cohort but steroid-sparing drugs may represent an alternative treatment. Mycophenolate mofetil (MMF) and sirolimus are effective agents in ES, as a way of limiting steroid utilization [28–31]. Although use of these drugs is still limited in a neurological setting, MMF has been reported to be effective in neuro-sarcoidosis, acute inflammatory polyradiculoneuropathy, and multiple sclerosis [32–34]. In one small cohort, sirolimus improved multiple sclerosis lesions [35]. Further data are still required to optimize the management of these drugs. When a specific therapy is available based on the underlying PID, its use may prevent recurrences during steroid tapering and during prolonged treatment courses. The weaning of immunosuppressive drugs can be difficult and a sustained low dose may be required to control the neurological lesions.

Neurological involvement appeared late after the first cytopenia and concerned a particular subgroup, who were different from the “run-of-the-mill” patients with an AIC. This mostly concerned patients with ES, a population with a high probability of underlying PID [3, 36]. Other immunopathological manifestations were present in all cases but with few infectious manifestations, despite hypogammaglobulinemia and frequent abnormal lymphocyte phenotype. These elements distinguish those patients from early onset hypogammaglobulinemia, which is usually revealed by infectious manifestations [37].

A PID was identified in three patients. Autoimmunity as a common feature of DiGeorge syndrome and ES has been reported [38–40]. To the best of our knowledge, no dysimmune neurological involvement had been reported. Strikingly, two patients presented a CTLA4 deficiency. Mutations in the CTLA4/LRBA axis were recently described in patients with autoimmune organ injuries, AIC, hypogammaglobulinemia, and lymphadenopathy/splenomegaly [14, 41–44]. Neurological immune infiltration is not uncommon in patients carrying *CTLA4* mutations; this concerned 10 of the 133 patients in the largest cohort whereas in two series of patients carrying *LRBA* mutations, only 1/22 and 3/28 presented such involvement [14, 41, 42, 44–51]. The clinical, radiological and pathological features were similar to our cases [41–44]. The identification of these PID provides a unique opportunity for a specific treatment. A substantial clinical amelioration has been reported in patients treated by the Ig-CTLA4 fusion protein abatacept [14, 43, 51–53]. This effect has been specifically described in cerebral lesions [54].

In four cases, no pathological variant was identified. However, their phenotype is highly indicative of an underlying PID. It is plausible that in the near future, the identification of new PIDs or the description and functional analyses of new mutations will allow a better understanding the mechanism of their dysimmunity.

In conclusion, the development of neurological immunopathological manifestations in a patient who presented with an AIC in childhood strongly suggests an underlying PID. Those patients have to be researched from an internist’s perspective, concerning other organ immunopathological manifestations and with complete immunologic explorations. The precise pathophysiology of the neurological lesions observed in these patients are not yet fully understood. If the underlying PID can be diverse, our data suggest that a CTLA4 deficiency should be researched, notably because of its great therapeutic impact.

**Authorship contributions.** TP, BN, JLP, FRL, and NA designed the research, analyzed the data, and participated in writing the paper. HDLP reviewed the MRI. PV and AG reviewed the pathology samples. HF was the data manager and performed the statistical analyses. FRL performed the biology molecular analyses. BN, JLP, NA, GL, TL, HC, GM, MP, FM, OH, AM, MHu, HZ, MHa, JMD, and YP were in charge of the patients and participated in data and blood sample collection. All authors critically read the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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## Compliance with Ethical Standards

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