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Autoantibody status, neuroradiological and clinical findings in children with acute cerebellitis

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ABSTRACT

Background: Acute cerebellitis (AC) in children and adolescents is an inflammatory disease of the cerebellum due to viral or bacterial infections but also autoimmune-mediated processes.

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MOG antibodies
Children
Autoimmune

Objective: To investigate the frequency of autoantibodies in serum and CSF as well as the neuroradiological features in children with AC.
Material and methods: Children presenting with symptoms suggestive of AC defined as acute/subacute onset of cerebellar symptoms and MRI evidence of cerebellar inflammation or additional CSF pleocytosis, positive oligoclonal bands (OCBs), and/or presence of autoantibodies in case of negative cerebellar MRI. Children fulfilling the above-mentioned criteria and a complete data set including clinical presentation, CSF studies, testing for neuronal/cerebellar and MOG antibodies as well as MRI scans performed at disease onset were eligible for this retrospective multicenter study.
Results: 36 patients fulfilled the inclusion criteria for AC (f:m = 14:22, median age 5.5 years). Ataxia was the most common cerebellar symptom present in 30/36 (83 %) in addition to dysmetria (15/36) or dysarthria (13/36). A substantial number of children (21/36) also had signs of encephalitis such as somnolence or seizures. In 10/36 (28 %) children the following autoantibodies (abs) were found: MOG-abs (n = 5) in serum, GFAPα-abs (n = 1) in CSF, GlyR-abs (n = 1) in CSF, mGluR1-abs (n = 1) in CSF and serum. In two further children, antibodies were detected only in serum (GlyR-abs, n = 1; GFAPα-abs, n = 1). MRI signal alterations in cerebellum were found in 30/36 children (83 %). Additional supra- and/or infratentorial lesions were present in 12/36 children, including all five children with MOG-abs. Outcome after a median follow-up of 3 months (range: 1 a 75) was favorable with an mRS ≤2 in 24/36 (67 %) after therapy. Antibody (ab)-positive children were significantly more likely to have a better outcome than ab-negative children (p = .022).
Conclusion: In nearly 30 % of children in our study with AC, a range of abs was found, underscoring that autoantibody testing in serum and CSF should be included in the work-up of a child with suspected AC. The detection of MOG-abs in AC does expand the MOGAD spectrum.

Abbreviations

AC	Acute Cerebellitis
e.g.	example given
MRI	Magnetic Resonance Imaging
ACA	Acute Cerebellar Ataxia
AE	Autoimmune Encephalitis
MOG	Myelin-oligodendrocyte-glycoprotein
MOGAD	Myelin-oligodendrocyte-glycoprotein-associated disease
CSF	cerebrospinal fluid
OCBs	oligoclonal bands
CBA	cell based assay
TBA	tissue based assay
mGluR	metabotropic glutamate receptor
GFAP	glial fibrillary acidic protein
GlyR	Glycine Receptor
CV2/CRMP5	CV2/collapsin response mediator protein 5
CASPR2	contactin-associated protein-like 2
DNER/Tr	Delta/Notch-like epidermal growth factor-related receptor
GAD65	glutamic acid decarboxylase 65-kDa isoform
NMDAR	N-methyl-D-aspartate receptor
GABAAR	gamma (γ)-aminobutyric acid-A receptor
GABABR	gamma (γ)-aminobutyric acid-B receptor
IgLON5	immunoglobulin-like cell adhesion molecule 5
AMPAR	Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor
LGI1	Leucine-rich glioma-inactivated protein 1
Zic4	Zic family member 4 (zinc finger protein of the cerebellum 4)
DPPX	Dipeptidyl Aminopeptidase-Like Protein 6
FLAIR	Fluid Attenuated Inversion Recovery
DWI	Diffusion Weighted Imaging
ACD	Apparent Diffusion Coefficient
EPEC	Enteropathogenic *Escherichia coli*
Ab	Autoantibody
mRS	Modified Ranking Scale/Score
ADS	Acute Demyelinating Syndrome
ADEM	Acute Disseminated Encephalomyelitis
ON	Opticus Neuritis
CA	Cerebellar Ataxia
ACE	Acute Cerebellitis with Encephalitis
IVMP	intravenous methylprednisolone

1. Introduction

Acute cerebellitis (AC) in childhood and adolescence is an inflammatory disease of the cerebellum that can occur in the context of infections, but also through immune-mediated processes. Although the clinical presentation can be highly variable, AC often manifests as an acute cerebellar dysfunction with stance, gait, and truncal ataxia, dysmetria or dysarthria. Additional symptoms can include encephalopathy, vomiting, headache, or fever indicating a more severe course of the disease [1].

Although it has been agreed upon recently to use the term AC mainly for the clinical cerebellar syndrome with evidence of inflammation on magnetic resonance imaging (MRI), differentiation between AC and acute cerebellar ataxia (ACA) -usually postinfectious and without MRI changes-remains difficult [1].

Research in the field of neuroinflammatory diseases has made significant progress with autoantibody (ab) testing becoming increasingly important in the diagnosis of neuroinflammatory syndromes such as autoimmune encephalitis (AE) and myelin-oligodendrocyte-glycoprotein (MOG)-antibody-associated disease (MOGAD) [2,3]. Also in patients with AC or ACA autoantibodies (abs) such as homer-3 [4] or metabotropic glutamate receptor (mGluR) -abs were recently described [5–7].

The primary objective of this study was to evaluate the ab status in children with AC, in addition to the radiological presentation and clinical outcome.

2. Material and methods

2.1. Patient recruitment and inclusion criteria

Between 2010 and 2023 63 children from 22 different hospitals in Germany, Austria, and Switzerland were referred with a suspected diagnosis of AC for a second opinion and further work-up either to the Division of Neuropathology and Neurochemistry, Department of

Neurology, Medical University of Vienna, Austria or included in two ongoing studies collecting children with a first acute demyelinating attack (ADS) (BIOMARKER-Study) or the Generate registry (see Fig. 1).

For this retrospective multicenter study, demographic, clinical, and laboratory data were collected from patients' medical records and patients had to meet the following inclusion criteria: Presentation with symptoms compatible with acute/subacute cerebellar syndrome (e.g. ataxia, dysarthria, or dysmetria) and cerebellar evidence of inflammation on MRI or additional signs of inflammation in the cerebrospinal fluid (CSF) such as pleocytosis and/or positive oligoclonal bands (OCB) or positive ab-status in case of negative cerebellar MRI. All patients must have had detailed ab testing in addition to MRI-imaging at disease onset. The outcome was assessed with the modified ranking score (mRS) (mRS 0 = no symptoms, mRS 1 = no significant disability despite symptoms, mRS 2 = slight disability, mRS 3 = moderate disability, mRS 4 = moderately severe disability, mRS 5 = severe disability, mRS 6 = death) at disease nadir and at last follow-up. The study was approved by the Institutional Review Board of the Medical University of Vienna (EK 1123/2015 and 1636/2019) and Ethics Committee of the Witten/Herdecke University, Germany (BIOMARKER-Study number AN4059, Generate-Study number 208/15).

2.2. Antibody status

Information on ab status was taken from patient records. Ab-testing was performed in the following laboratories: Institute for Clinical Chemistry (Central Laboratory), University Kiel (F. Leypoldt), the Division of Neuropathology and Neurochemistry, Department of Neurology, Medical University Vienna (R. Höftberger), and the Division for Experimental Neurology, Medical University Innsbruck (M. Reindl). Test methods followed the latest laboratory standards with an initial screening test and a second confirmation test using tissue-based assays (TBA) (immunofluorescence testing or staining on paraformaldehyde-fixed rat brain sections) and cell-based assays (CBA) as well as immunoblot testing. In-house assays were performed with standardized protocols that are regularly validated with inter-laboratory ring trials [8–10]. MOG- and glycine receptor-ab testing was performed with live in-house CBAs, and anti-GFAPα-antibodies were tested with a fixed in-house CBA and tissue-based assay confirmation. MOG abs were screened in serum and if available CSF with a CBA using full-length human MOG. Serum samples were scored according to a high-titer cut-off as moderately positive (titer 1:160–1:320) and strongly positive (titer 1:640 and higher). To exclude false positive results we used an IgG(Fc) secondary antibody [11]. In general, the following intracellular and anti-neuronal surface abs were determined in CSF and/or serum using a combination of commercial and in-house CBA and TBA as previously described by the participating laboratories [11–13]: HuD, Yo, Ri, CV2/CRMP5, amphiphysin, Ma1/2, Sox1, Tr/DNER, Zic4, GAD65, and PKCgamma. NMDAR, GABABR, AMPAR 1/2, DPPX, LGI1, and CASPR2, GABAAR, IgLON5, neurexin3alpha, mGluR5, mGluR2, and mGluR1, MOG- and glycine receptor-ab (GlyR), and anti-GFAPα-abs.

2.3. MR-imaging

All children included in the study had MRI scans of the first episode, which were sent to the Department of Radiology at the Children's Hospital, Datteln, Germany for evaluation by two independent observers unaware of the clinical presentation and the ab status. In 24/36 children the initial MRI was performed on scanners with a field strength of 1.5 T and in 12/36 children with 3.0 T scanners. In case of discordant results, the MRIs were reviewed together, and a common decision was made. The following criteria for the MRI evaluation were selected: a) localization of the findings such as [1] bilateral [2], unilateral [3], including vermis, such as [1] white matter, and [2] cortex; b) quality of lesions defined as [1] edema [2], swelling [3], T2-weighted/Fluid Attenuated Inversion Recovery (FLAIR) signal hyperintensity; c) evaluation of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC); d) presence of contrast medium enhancement; e) presence of cerebellar tonsil herniation; f) presence of spinal involvement. All criteria were applied to both the cerebellum and other supratentorial or infratentorial regions.

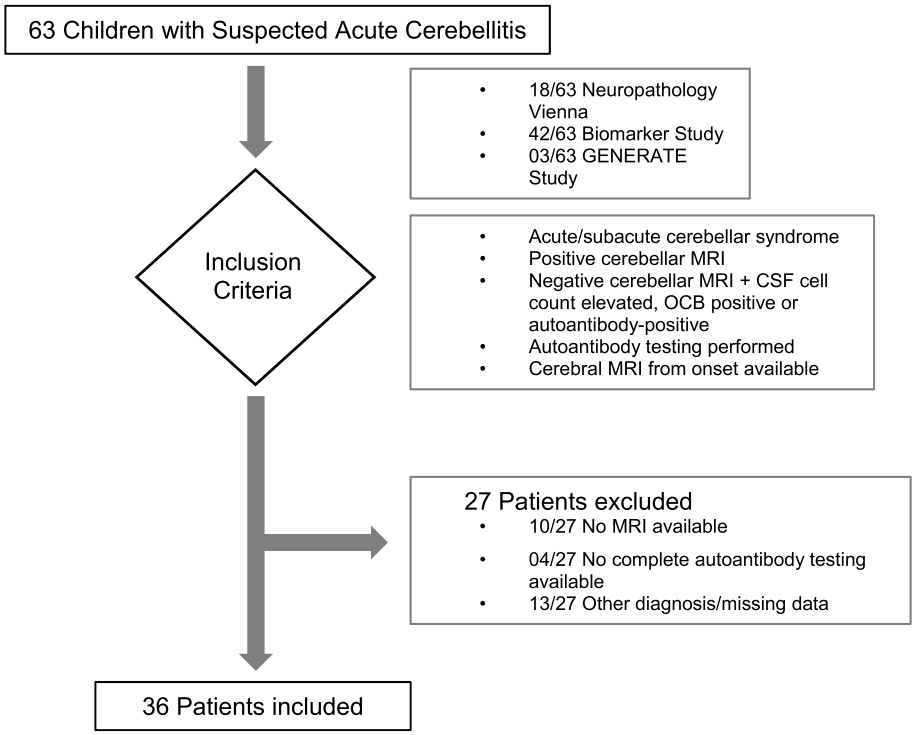

Fig. 1. Flowchart Patient Recruitment: Inclusion and Exclusion Process. **CSF** Cerebrospinal fluid **MRI** Magnetic resonance imaging.

2.4. Neuropathological evaluation of two biopsies and one autopsy from children with AC

Formalin-fixed paraffin-embedded 5 μm thick sections were stained with hematoxylin and eosin (H&E) and Luxol Fast Blue. Immunohistochemistry was performed with an avidin–biotin-complex method, using primary antibodies against CD3 (1:500, Leica Biosystems), CD4 (1:100, DAKO, Denmark), CD8 (1:50, DAKO, Denmark), CD20 (1:400, DAKO, Denmark), CD79a (1:50, DAKO, Denmark), CD68 KP1 (1:100, DAKO, Denmark), CD138 (1:200, Cell Marque), HLA-DR (1:100, DAKO Denmark), MHC class I (HC10; 1:2000; from Hidde Ploegh, Stam et al., 1990), granzyme B (1:1000, Neomarkers), pSTAT1 (1:2000, Cell Signaling), glial fibrillary acidic protein (GFAP, 1:100, DAKO, Denmark), and calbindin D (1:1500, Thermo Scientific).

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS. Metric data are described using mean [SD] and range if normally distributed or median and maximum and minimum values for skewed metric or ordinal data. Additionally, 95 % confidence intervals were calculated. Categoric data are presented as absolute frequencies and percentages. Crosstabs and χ^2 tests were used to compare groups regarding nominal data. A p-value $\leq$5 % (p = .05) indicated significant results. To avoid an increasing error of the second type, we did not perform multiplicity corrections. All analyses were performed using SPSS Statistics for Mac, Version 27.0 (IBM).

3. Results

3.1. Patients

In a first step 63 children with suspected AC were identified. Finally, 36 children met the inclusion criteria including symptoms compatible with acute/subacute cerebellar symptoms (e.g. ataxia, dysarthria, or dysmetria), evidence of cerebellar inflammation on MRI signs of inflammation in CSF (pleocytosis and or/positive OCBs) or a positive abs-status. In addition, all patients had MRI scans from the initial episode. The cohort consisted of 22 boys (61 %) and 14 girls (39 %) with a median age at onset of 4.8 years (range: 2–17 years). All clinical findings, the autoantibody status, neuroradiological features, and the outcome of all 36 children with AC are summarized in Table 1.

Ataxia either at onset or during the course of the disease was the most common symptom (30/36, 83 %) followed by dysmetria, dysdiadochokinesia (15/36, 42 %) or dysarthria (13/36, 36 %). Ataxia was present in 21/36 (58 %) children at the onset of the disease. Headache (15/36, 42 %), fever (16/36, 44 %), and signs of encephalitis (21/36, 58 %) with symptoms ranging from somnolence (17/21, 81 %), behavioral abnormalities (8/21, 38 %), and seizures (7/21, 33 %) were also often present. Some children initially presented with somnolence (9/36, 25 %), or additional seizures (7/9, 77 %) but subsequently developed marked cerebellar symptoms such as gait ataxia (9/9, 100 %), dysmetria (4/9, 44 %) or dysarthria (3/9, 33 %) in the following days after admission.

CSF pleocytosis (>5 white cell count/μl) was recorded in 23/36 (64 %). Protein levels (>40 mg/dl) were elevated in 14/36 (39 %) children. OCBs were positive in 10/36 (28 %). Electroencephalography was performed in 29/36 (81 %) children, showing pathological changes in 14/36 (48 %) children ranging from focal (6/29, 21 %) or diffuse (7/29, 24 %) slowing to epileptogenic discharges (1/29, 3 %).

In 21/36 (58 %) children, an infection within the last four weeks was reported by the parents. In two children CSF- polymerase chain reaction (PCR) analysis revealed evidence of an unclassified Enterovirus with high IgM ab titers for Echovirus in serum, with one having additional elevated IgM-ab titers for Coxsackie virus A and B. Another child's CSF analysis revealed high ab titers for IgM- M. *pneumoniae*, without serum abs. Detection of adenovirus via PCR in CSF, stool sample, and pharyngeal swab was found in one child. Further evidence of pathogens was found in six further children: 4/6 showing positive results via PCR/culture of stool samples (enterovirus (n = 1), enteropathogenic *Escherichia coli* (EPEC) (n = 1), Rotavirus (n = 2)), and in pharyngeal swab (Influenza A (n = 1), Influenza B (n = 1), Group A Streptococcus (GAS) (n = 1)) in the remaining three. Solely elevated serum ab titers were found in two children (M. *pneumoniae*-IgM, -IgG, and -IgA (n = 1), Enterovirus-IgM (n = 1)). One child showed evidence for VZV reactivation during disease course (increased VZV-immunoglobulin G (IgG)-titers in CSF and PCR amplification of VZV sequences in formalin-fixed and paraffin-embedded tissue from cerebellar biopsy). Among the pathogen-positive children, two children were also ab-positive: one child with a positive GlyR-ab tested positive for Enterovirus in CSF via PCR and had additional elevated IgM-ab-titers for Echovirus in serum. The other one was a MOG-ab-positive child with elevated Enterovirus-IgM-ab-titers in serum.

3.2. Autoantibody findings

In 10/36 (28 %) children with AC, a range of abs in serum and/or CSF samples were detected: MOG-abs (n = 5) in serum, GFAPα-abs (n = 1) in CSF, GlyR-abs (n = 1) in CSF, mGluR1-abs (n = 1) in CSF and serum. In two children, abs were detected only in serum (GlyR-abs, n = 1; GFAPα-abs, n = 1). In 26/36 (72 %) children no abs in serum nor CSF were detected.

The clinical characteristics of ab-positive AC did not differ from those with ab-negative AC (Table 1), except that ab-positive children had significantly more supra- or infratentorial lesions in MRI (7/10, 70 % versus 5/20, 25 %; p = .015). Two of seven (29 %) ab-positive patients with MRI lesions beyond the cerebellum showed clinical signs of encephalitis (one MOG-ab- positive, one mGluR1-ab-positive).

3.2.1. Clinical features of MOG-ab-positive patients

Serum MOG-abs were found in 5 children (three boys and two girls) (5/10, 50 %) with a median age at onset of 4 years (range 2.4–6.3 years). All patients had gait ataxia. One child had fever and one showed clinical signs of encephalitis with behavioral changes in addition. Another MOG-ab-positive patient without clinical signs of encephalitis at presentation developed a pathological EEG during the disease course with diffuse slowing, which resolved completely after remission of the disease.

3.3. MR-imaging findings

MR-imaging revealed cerebellar involvement in 30/36 children (83 %). In 22/30 (73 %) children bilateral signal changes were found often affecting white matter and cortical structures simultaneously. In six cases (6/30, 20 %) additional involvement of the vermis was noted. In 8/30 (27 %) children only unilateral involvement was found affecting cerebellar white matter in one child, cortical structures in four, or both in three children.

Inflammatory lesions in the cerebellum usually appeared as signal hyperintensities in FLAIR and T2 images. Areas of restricted diffusion (high signal on diffusion weighted imaging (DWI)) were found in 21/36 (58 %) children in the absence of low signal on apparent diffusion coefficient (ADC) indicating vasogenic edema. Only in 4/21 (19 %) children, additional low signals on ADC were noted indicating cytotoxic injury (Fig. 2). Moderate swelling of the cerebellum of one or both hemispheres was seen in 17/36 (47 %) children with cerebellar herniation in seven (7/17, 41 %).

Six of 36 children (17 %) with AC did not show any signs of cerebellar involvement on MRI with five children (5/36, 14 %) having a completely overall unremarkable MRI. The remaining child -with positive GFAPα-abs in CSF- had supratentorial lesions involving white matter and basal ganglia in the absence of cerebellar findings while the clinical presentation was characterized by severe ataxia.

Table 1
Clincial findings, autoantibody status and neuroradiological features including outcome in 36 children with Acute Cerebellitis.

Pat. Nr.	Age/ onset	Sex	Autoantibody status	Clinical presentation	MRI: Cerebellar lesions	Additional MRI lesions	CSF findings	Pathogen detection	mRS pre Tx	mRS last Fu
1	4,0	m	MOG (S)	vomiting, fever, ataxia, hemiparesis	unil. white matter lesions + vasogenic edema	white matter, thalamus, subcortical	none	none	4	1
2	4,0	m	MOG (S)	ataxia, torticollis, cephalea	unil. cortical lesions	diffuse white matter, CC	pleocytosis, protein↑	none	3	0
3	4,0	f	MOG (S)	vomiting, fatigue, ataxia, torticollis, fever	unil. white matter/ cortical lesions	subcortical/ cortical white matter, BG	pleocytosis, protein↑	S: IgM Enterovirus abs	4	1
4	2,4	m	MOG (S)	ataxia, dysarthria, anarthria	bil. white matter lesions	cerebellar peduncles, thalamus, BG	none	none	3	0
5	3,2	m	mGluR1 (S + CSF)	ataxia, behavioural changes	none	none	pleocytosis, pos OCB,	none	4	1
6	7,9	f	GlyR (S + CSF)	ataxia, vomiting, cephalea	unil. cortical lesions with vasogenic edema/ swelling	none	pleocytosis, pos OCB	CSF: Enterovirus (PCR); S: Echovirus IgM abs	3	1
7	2,7	m	GlyR (S + CSF)	ataxia, dysmetria, fever, cephalea, URI	bil. white matter lesions + vasogenic edema/swelling	white matter, cerebellar peduncles	pleocytosis protein↑	none	3	0
8	3,3	m	GFAP (CSF)	ataxia, dysmetria, URI	none	white matter, BG	pleocytosis protein↑	none	4	1
9	4,3	m	GFAP (S)	ataxia, dysmetria, dysarthria, behavioral changes	none	none	pos OCB	none	4	1
10	3,8	f	neg	fever, seizures, behavioral changes	bil. white matter lesions + vermis	none	pleocytosis, pos OCB,	CSF: adenovirus (PCR)	5	3
11	11,9	m	neg	ataxia, cephalea, behavioral changes	bil. cortical lesions + vasogenic edema/ swelling	none	none	none	3	2
12	14,2	f	neg	nausea, ataxia, dysmetria, mutism, fever, vigilance reduction, behavioral changes	bil. cortical lesions + vasogenic edema/ swelling	none	pleocytosis, protein↑	none	5	1
13	3,8	m	neg	vomiting, cephalea, poor vigilance with hypopnoe, bradycardia, hypertonus	bil. cortical lesions + vasogenic edema/ swelling, cerebellar herniation, hydrocephalus	none	pleocytosis, protein↑	none	4	0
14	5,7	m	neg	cephalea, vigilance reduction, vomiting, seizures, ataxia, dysmetria	bil. cortical lesions + vasogenic edema/ swelling, cerebellar herniation, hydrocephalus	none	none	none	5	3
15	7,0	m	neg	cephalea, vigilance reduction, vomiting	bil. cortical lesions + vasogenic edema/ swelling, CM enhancement, hydrocephalus	none	pleocytosis, protein↑	none	4	1
16	8,3	m	neg	URI, fever, ataxia, dysarthria, dysmetria, vigilance reduction	bil. white matter lesions + vasogenic edema	none	intrathecal IgA synthesis	S: C. pneumoniae IgG/IgA; pharyngeal swab: Influenza B (PCR)	4	2
17	6,7	m	neg	fever, dysarthria, vigilance reduction, behavioral changes	bil. cortical lesions + vasogenic edema/ swelling	none	pleocytosis	none	5	3
18	2,1	m	neg	respiratory tract infection, fever, ataxia. dysmetria, dysarthria	bil. white matter/ cortical lesions	none	pleocytosis, pos OCB	CSF: IgM M. *pneumoniae* abs	4	1
19	9,2	m	neg	cephalea, nausea, vomiting, fever, ataxia, dysmetria	unil. cortical lesion + vasogenic edema/ swelling	none	pleocytosis, intrathecal IgG + IgM synthesis, pos OCB	CSF: Enterovirus (PCR); serum: Echovirus-IgM, Coxsackie A-IgM, Coxsackie B-IgM abs	3	1
20	7,5	f	neg	cephalea, vomiting, vigilance reduction, ataxia, seizures	bil. cortical lesions, cerebellar herniation, hydrocephalus	none	pleocytosis, protein↑	S: M. pneumoniae IgM, IgG, IgA abs	3	0
21	3,5	f	neg	vigilance reduction, mutism, tremor, ataxia, seizures	bil. white matter lesions + cytotoxic edema/swelling, hydrocephalus	none	pleocytosis, protein↑	stool: Rotavirus (PCR)	5	4

(*continued on next page*)

Table 1 (*continued*)

Pat. Nr.	Age/ onset	Sex	Autoantibody status	Clinical presentation	MRI: Cerebellar lesions	Additional MRI lesions	CSF findings	Pathogen detection	mRS pre Tx	mRS last Fu
22	2,0	f	neg	fever, vomiting, diarrhea, seizures, ataxia, dysarthria, vigilance reduction, behavioral changes	bil. cortical lesions + vasogenic edema	none	none	stool: EPEC (culture)	4	3
23	7,7	m	neg	URI, fever, vomiting, diarrhea, seizures, ataxia, vigilance reduction	bil. cortical lesions + vasogenic edema/ swelling, cerebellar herniation, obstructive hydrocephalus	white matter, CC, BG	none	pharyngeal swab: Influenza A (PCR)	5	4
24	6,1	f	neg	vomiting, fever, vigilance reduction, dysarthria, ataxia, tremor	bil. white matter lesions + vasogenic edema	CC	pleocytosis, protein↑	pharyngeal swab: Streptococcus A (culture)	4	3
25	2,1	m	neg	fever, vigilance reduction, ataxia	bil. white matter/ cortical lesions	BG, CC, thalamus	pleocytosis, intrathecal IgM + IgA synthesis	stool: Enterovirus (PCR)	4	1
26	7,9	f	neg	vomiting, cephalea, ataxia, dysmetria, vigilance reduction	unilat. cortical lesions + vasogenic edema/ swelling	none	pleocytosis, protein↑	none	5	3
27	6,2	m	neg	URI, ataxia, dysmetria	unilat. white matter/ cortical lesions + vasogenic edema, + CM	none	pleocytosis, pos OCB	none	4	2
28	3,8	m	neg	vigilance reduction, behavioral changes seizures, dysarthria	bil. white matter/ cortical lesions + cytotoxic edema/ swelling, + CM	none	pos OCB	none	5	2
29	17,6	m	neg	ataxia	bil. white matter/ cortical lesions + vasogenic edema/ swelling	none	pleocytosis	none	2	2
30	7,4	m	neg	cephalea, vomiting, ataxia	bil. white matter/ cortical lesions + vasogenic edema/ swelling, cerebellar herniation	white matter, cortical/ subcortical	pleocytosis	none	2	0
31	13,4	f	neg	cephalea, fever, nausea, dysarthria, acute vigilance reduction	bil. cortical lesions + vasogenic edema/ swelling + vermis, cerebellar herniation, hydrocephalus	white matter pons	protein↑, pos OCB	S: VZV-IgG abs; cerebellar biopsy: VZV	2	5
32	2,5	m	neg	nausea, ataxia, URI	none	none	pleocytosis	none	4	3
33	5,1	f	neg	ataxia, dysmetria, tremor, dysarthria, cephalea	none	none	pleocytosis, pos OCB	none	4	3
34	3,6	f	neg	ataxia, fever, vigilance reduction	none	none	pleocytosis	none	4	1
35	6,3	f	neg	cephalea, vomiting, ataxia	unilat. white matter/ cortical lesion + vasogenic edema	none	none	none	3	1
36	4,1	f	neg	cephalea, vomiting, somnolence, behavioral changes, unable to walk, marked encephalopathy	bil. white matter/ cortical lesions + vasogenic edema, cerebellar herniation, obstructive hydrocephalus	none	pleocytosis, protein↑	stool: Rotavirus (PCR)	5	6

MRI magnetic resonance imaging CSF cerebrospinal fluid mRS modified ranking score Tx therapy Fu follow-up m male f female MOG Myelin oligodendrocyte protein S Serum unil. Unilateral CC Corpus callosum bil. Bilateral BG Basal ganglia IgM/A/G Immunoglobulin M/A/G C. pneumoniae Chlamydophila pneumoniae M. *pneumoniae* mycoplasma *pneumoniae* abs antibodies mGluR1 metabotropic glutamate receptor type 1 OCB oligoclonal bands GlyR Glycine receptor PCR polymerase chain reaction URI upper respiratory tract infection GFAP glial fibrillary acidic protein neg negative pos positive CM contrast medium enhancement VZV Varicella zoster virus.

Studying the relationship between ab status and neuroradiological features, statistical analysis showed significantly more unilateral manifestation of AC in the group of ab-positive children (5/10, 50 %) than in the ab-negative group (3/26, 12 %) (p = .027). Vice versa, ab-negative children showed significantly more often bilateral manifestation (20/26, 77 %) compared to ab-positive children (2/10, 20 %) (p = .006).

Fifteen of 36 children (42 %) presented with supra- or infratentorial lesions. Nine of 15 children (30 %) had supratentorial lesions, which involved white matter (n = 8), corpus callosum (n = 3), and/or basal ganglia region (n = 4), as well as cortical/subcortical (n = 2) or thalamus (n = 2). Five of 15 children (17 %) had infratentorial lesions in the pons or peduncular region. Other infratentorial lesions were more likely to be found in the ab-positive group.

3.3.1. *Neuroradiological features of MOG-ab-positive patients with AC*

Four children (4/5, 80 %) had a unilateral (Figs. 2 and 3), and one

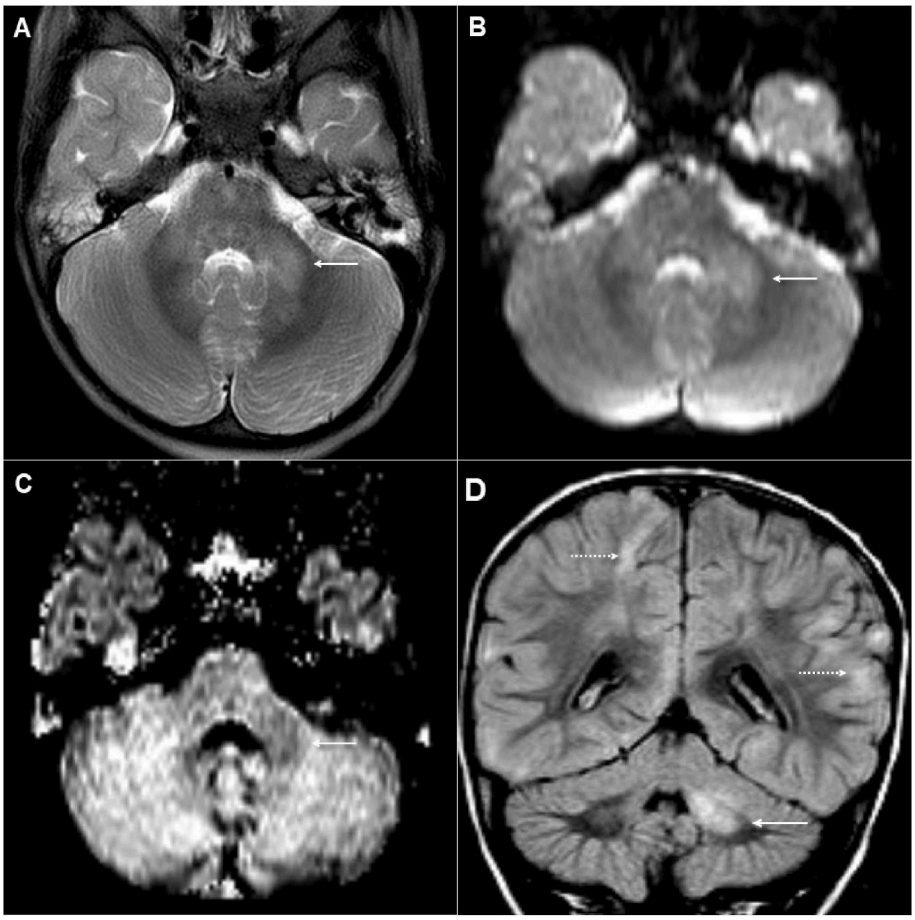

Fig. 2. Cerebral MRI of a 2.4-year-old boy (Table 1, Pat. 4) with signs of acute cerebellitis including gait ataxia and dysarthria who was tested positive for serum MOG-antibodies. The first image shows a left unilateral white-matter cerebellar lesion (white arrow) in the middle peduncle extending into the left central white-matter (A. T2-weighted, axial). Diffusion-weighted imaging shows a high signal (white arrow) with a low ADC-signal indicating (white arrow) diffusion restriction (B, C). In addition to the unilateral white matter cerebellar lesion (white arrow) several cortical and subcortical lesions were noted (white dotted arrows) (D, T2-weighted, coronal).

child (1/5, 20 %) had bilateral involvement of the cerebellum. In addition, two (2/5, 40 %) had lesions in the cerebellar white matter, one (1/5, 20 %) in the cerebellar cortex, and two (2/5, 40 %) in both. All demonstrated FLAIR/T2-hyperintensity with two of them showing additional vasogenic edema with diffusion restriction in the DWI sequence. One child demonstrated contrast medium enhancement of the cerebellar lesion with no contrast medium enhancement elsewhere. All patients had additional supra- or infratentorial lesions ranging from hazy signal hyperintensities in the thalamus (n = 2), corpus callosum (n = 1), basal ganglia (n = 1), or other diffuse white matter regions (n = 3). One child had spinal involvement in addition (see Fig. 4).

3.4. Outcome

The outcome was assessed with the mRS at disease nadir and follow-up. Referring physicians were asked to determine the mRS before and after therapy or according to the information available from the medical records by the authors. The median period of follow-up in our cohort was 4 months (range: 1 month-75 months).

Children were treated with different immunomodulatory agents including intravenous corticosteroids (20/36, 56 %), oral steroids (17/36, 47 %), intravenous immunoglobulins (10/36, 28 %), or with the immunomodulator rituximab (3/36, 8 %). Most children received antibiotics and/or antiviral medications and 5/36 (14 %) children received anti-seizure therapy. In the ab-positive group, 80 % (8/10) were treated with steroids (intravenous and/or oral) in comparison to 62 % (16/26) in the ab-negative group. Oral steroids were applied more often in the ab-positive group (70 %; 7/10) than in the ab-negative group (35 %; 9/10). Regarding intravenous steroids, no difference in application frequency could be observed (ab-positive group: 6/10, 60 %; ab-negative group: 13/26, 50 %). If steroids were applied, there were no differences in dosage or length of therapy in most children. Statistical analysis showed no significance in comparing treatment in both groups.

Initially, most children presented with moderate to severe symptoms at onset of disease (median mRS before therapy = 4) with the following distribution: mRS 2 (n = 3); mRS 3 (n = 9); mRS 4 (n = 15); mRS 5 (n = 8); mRS 6 (n = 1).

A favorable outcome was defined as a mRS of less than or equal to 2 which was present in most children (24/36, 67 %), demonstrating an overall good outcome in our cohort of children with AC.

3.4.1. Severe courses of AC

Nine children (9/36, 25 %) presented with a severe form of AC (mRS 5; all ab-negative). Six out of nine children (67 %) presented with ataxia and additional clinical signs of encephalitis such as seizures (n = 5), behavioral changes (n = 3), and most commonly encephalopathy (n = 7). Four (4/9, 44 %) had fever, two (2/9, 22 %) headache and six (6/9, 67 %) had other cerebellar symptoms.

Five of these 9 children (56 %) had a preceding infection and three of them (33 %) had evidence of a preceding or ongoing infection in CSF and serum (adenovirus, n = 1)), stool (rotavirus, n = 2; adenovirus, n = 1), and/or pharyngeal swab (influenza A virus, n = 1, adenovirus, n = 1).

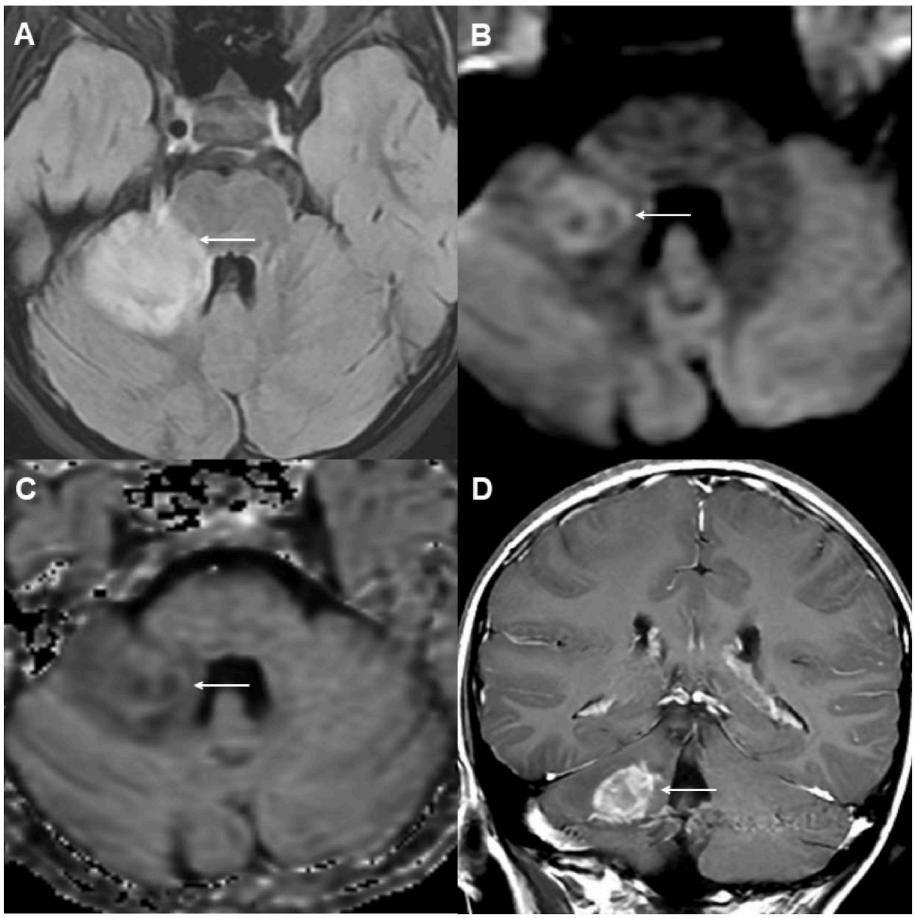

Fig. 3. Cerebral MRI of a 6.3-year-old girl (Table 1, Pat. 35) presenting with recurrent headache and vomiting, ataxia and visual problems who was also tested positive for MOG-antibody. A. First image reveals a right cerebellar lesion affecting the white matter and cortical region (white arrow) (A, T2-Flair, axial). B. The lesion has a high central white-matter signal on DWI (white arrow) and low corresponding ADC signal indicative of cytotoxic injury (B, DWI axial; C ADC, axial. Gadolinium enhancement indicating disturbance of blood-brain barrier in the central white matter was positive (D, T1-weighted, coronal, white arrow).

Imaging studies revealed marked cerebellar changes in all nine children. Eight children (8/9, 89 %) had a bilateral AC, mostly affecting the cortex (6/9) with signs of vasogenic (n = 5) or cytotoxic injury (n = 2) and swelling of one or both hemispheres (8/9). Only one child showed additional supratentorial lesions. Seven children (7/9, 78 %) presented ataxia and/or other cerebellar symptoms, and two (2/9, 22 %) (1/2 with positive rotavirus detection in stool sample) developed cerebellar mutism. In 5/9 children (56 %) CSF-pleocytosis was detected ranging from 6 to 108 cells/µl.

Looking at the neuroradiological manifestations, eight of 36 children (22 %, all ab-negative) developed severe neurological complications such as signs of obstructive hydrocephalus (8/8) or MRI findings indicative of cerebellar herniation on MRI (7/8), accompanied by encephalopathy (n = 6), seizures (n = 3), headache (n = 6), or nausea/vomiting (n = 3). Five children (5/36, 14 %) needed surgical intervention such as external ventricular drainage or additional decompressive craniectomy in one. No child needed a permanent ventriculoperitoneal shunt.

The outcome in this group of children with neuroradiological complications (n = 8) was heterogenous with the following distribution: mRS 0 (n = 2), mRS 1 (n = 1), mRS 3 (n = 1), mRS 4 (n = 2), mRS 5 (n = 1), mRS 6 (n = 1). The child with an mRS of 5 after therapy had a craniectomy and suffered severe neurological sequela with a locked-in syndrome (Table 1, Pat. 31). The latter child died due to fulminant herniation (Table 1, Pat. 36).

All children with severe complications were ab negative.

3.4.2. *Outcome of ab-positive versus ab-negative patients*

Ab-positive children had a significantly better outcome defined by an mRS of 1 or 0 at last follow-up compared to those without abs (100 % versus 38 %; p = .042).

MOG-ab-positive children showed moderate to severe impairment at onset of disease with mRS scores of 3–4. The clinical outcome was good in all 5 children with a mRS of 1 or less.

In 12/26 (46 %) of the ab-negative children, mRS at last follow-up was more than 2 (mRS 3 (n = 8), mRS 4 (n = 2), mRS 5 (n = 1), mRS 6 (n = 1)) indicating significant restrictions in activities of daily life. Nine children continue to have mild ataxia or speech impairment, two had more severe forms with more severe trunk and gait ataxia, dysmetria or dysarthria.

3.5. *Neuropathological findings*

From one patient, who died due to the complication of AC, post-mortem brain tissue was available (Table 1, Pat. 36). In addition, three children, who presented with sudden onset of AC and MRI features were suggestive of a tumor at the initial assessment, underwent cerebellar biopsy. From two of them, sufficient tissue was available, and these children were included in our neuropathological study (Table 1, Pat. 14, and 30).

Autopsy study was performed on a 4-year-old girl, who was admitted with vomiting and fever due to a presumed respiratory tract infection and somnolence. The initial cMRI was overall reported as normal. A lumbar puncture revealed a pleocytosis and an elevated protein. In

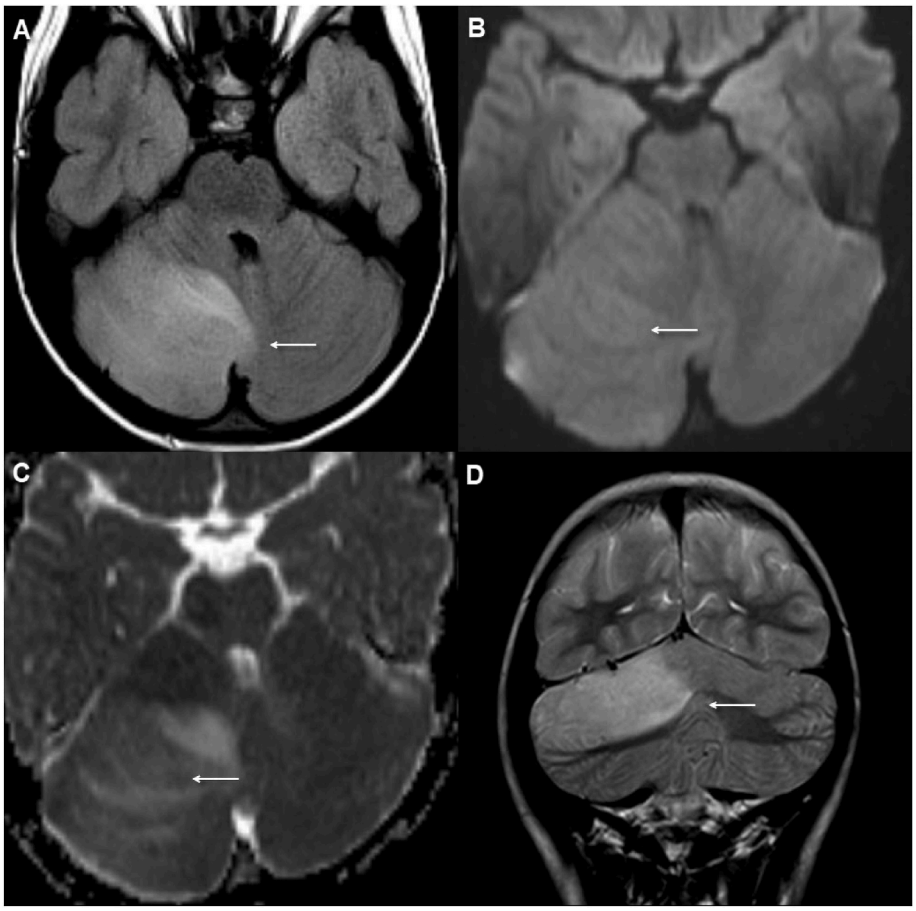

Fig. 4. Cerebral MRI of a 7.9-year-old girl (Table 1, Pat. 6) presenting with headache, nausea, and ataxia who tested positive for serum and CSF GlyR-antibodies revealed a right unilateral cerebellar lesion (white arrow) with minor midline displacement (A, T2-FLAIR, axial). The lesion shows mild central DWI-signal changes (white arrow) less pronounced in other parts of the lesion (B, DWI, axial) accompanied by minor ADC-signal alterations (white arrow) indicating diffusion restriction primarily in the central part of the lesion (C, ADC, axial). The right unilateral cerebellar lesion affecting mainly the cerebellar cortex (white arrow) is clearly seen in the T2 -weighted coronal image (D).

addition, the patient was found to have a rotavirus infection. The following day the patient deteriorated with increasing somnolence and was transferred to the ICU. MRI examination of the brain repeated 11 days after disease onset showed severe cerebellar edema in both hemispheres (Fig. 5A) with cerebellar herniation. Unfortunately, despite surgical intervention and intensive care treatment, the child passed away due to the fulminant disease course. Postmortem examination of the entire cerebellar hemispheric sections showed widespread areas of Purkinje cell loss and Bergmann gliosis affecting both hemispheres and tonsils while the vermis was spared (Fig. 5B–D). Inflammation consisted of mild meningeal and perivascular infiltrates of CD3, CD4, and CD8 positive T cells (Fig. 5E–G), and some CD20 and CD79a positive B cells and plasma cells (Fig. 5H and I). In addition, few parenchymal CD8-positive T cells were found in the molecular and granular layer of the cerebellar cortex. Marked reactive micro- and astrogliosis and some macrophages were found in the molecular layer of the cerebellar cortex. The cerebellar white matter was well preserved, the vessels showed mild perivascular inflammatory infiltrates. The dentate nucleus was unremarkable (data not shown).

Biopsies were derived from two patients (2 male; 6 and 7 years old) with AC and neuroimaging features thought to be a tumor by the treating physicians (Fig. 5J). None of the patients had received immunotherapy before the specimens were obtained. Both biopsies contained multiple small fragments of cerebellar cortex and leptomeninges. The inflammatory features observed in the autopsy were also found in the biopsies but were more intense and dominated by profound leptomeningeal and perivascular inflammation, composed of CD3, CD4, and CD8 positive T cells (Fig. 5K-M), abundant CD20 positive B cells (Fig. 5N), CD138 positive plasma cells, and monocytes. In addition, prominent microglia activation (Fig. 5O) and scattered CD8-positive T cells were found in the molecular layer (Fig. 5M). The cerebellar cortex showed a subtotal loss of Purkinje cells and Bergmann gliosis with clustered foci of glial cells with nuclear translocation of pSTAT1 (Fig. 5P).

4. Discussion

Our study shows that in up to one third of children with AC a spectrum of abs can be detected. We further found that children with AC and abs do have a more favorable clinical course and rarely presented with bilateral MRI changes of the cerebellum. Interestingly MOG-abs were the most frequently detected ab in our cohort of children with AC. MOG-abs are primarily found in children with acute disseminated encephalomyelitis (ADEM), transverse myelitis, or optic neuritis (ON) and relapsing forms such as recurrent ON [14]. Only recently selected cases were reported presenting primarily with acute ataxia and MOG-associated cerebellar inflammation on MRI [15] as well as one recurrent disease course of AC in a young adult with MOG-abs [16]. Typical MRI findings in MOGAD are large, hazy subcortical and deep white matter lesions in ADEM often also affecting the cerebellum or myelon. In the cerebellum large middle cerebellar peduncle lesions are often reported [17]. In our study, imaging revealed mostly unilateral

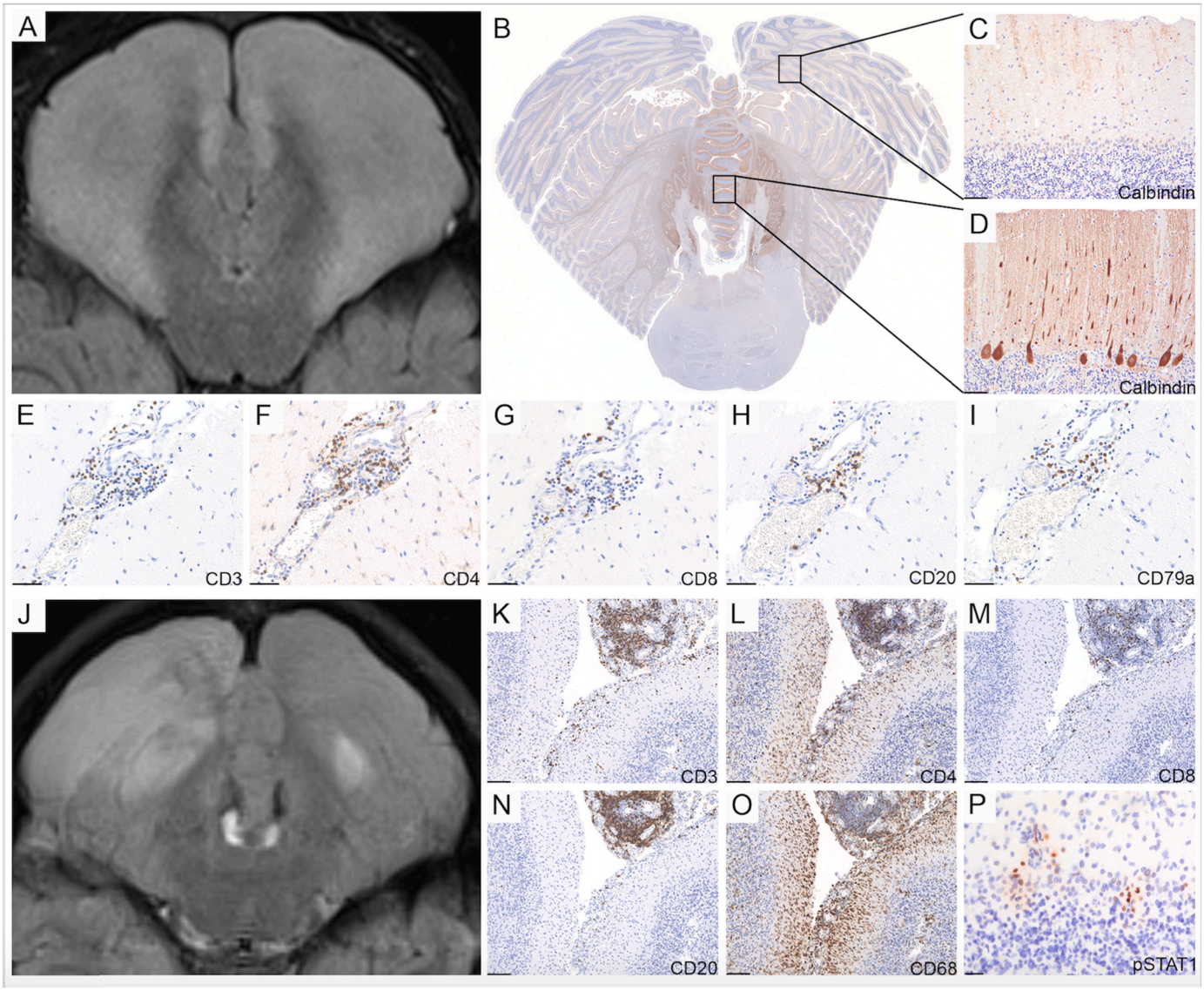

Fig. 5. Neuropathological findings in children with acute cerebellitis. MR-imaging of the cerebellum of a 4-year old girl, who subsequently died due to herniation reveals, a pronounced T2-weighted hyperintensity in both hemispheres (A; T2-weighted, axial). Topographic evaluation in post-mortem brain tissue shows widespread bi-hemispheric Purkinje cell loss and Bergmann gliosis with preservation of the vermis (A-D; rectangles in B enlarged in C and D; C: Purkinje cell loss and Bergmann gliosis in hemisphere; D: Purkinje cells preserved in vermis). Inflammation in the meninges is characterized by moderate numbers of $CD3^+$ (E), $CD4^+$ (F), CD8+T cells (G), and $CD20^+$ (H) and CD79a + B cells/plasma cells (I). Cranial MRI scan of a 7-year old boy, who subsequently underwent brain biopsy, reveals bilateral T2-weighted signal alterations affecting the cerebellar cortex (J, axial). The biopsy specimen shows pronounced inflammation with abundant $CD3^+$ (K), $CD4^+$ (L) and $CD8^+$ T cells (M) and $CD20^+$ B cells (N) in the meninges and some $CD8^+$ T cells in the parenchyma (M). Profound microglia activation including macrophages are seen in the molecular layer of the cerebellum (O). The cerebellar cortex shows clustered foci of glial cells with nuclear translocation of pSTAT1 (P). Scale bars: C–I: 50 μm; K–O: 100 μm; P: 30 μm.

cerebellar manifestation, as well as other supratentorial or infratentorial white matter lesions which is consistent with the previous reports. Two of our MOG-positive patients (2/5, 40 %) with AC had a relapsing course with at least one more event with symptoms similar to the initial clinical manifestation. Albeit rare MOGAD presenting with AC appears to be a distinct phenotype associated with additional supratentorial or infratentorial MOG-like lesions in the absence of other clinical features and should therefore be included in the differential diagnosis of AC.

Children described as being encephalopathic were severe cases which are summarized under “severe courses of AC 9/36” in chapter 3.4.1. with a fulminant disease course and changes in vigilance. These children all had an mRS at onset of 5. All of these children were ab-negative. Interestingly most of these children either showed a positive history of infection or showed evidence of infectious agents in CSF/serum/stool indicating a postinfectious diseases process. The cMRI only in one out of nine children showed additional supratentorial lesions not reminiscent of ADEM and the main neurological symptom in these children was ataxia or inability to walk. It has been reported that children with AC also can have clinical signs of encephalitis. For these children the term “cerebellitis plus” is often used. Therefore, we included these children in our cohort.

Interestingly all MOG serum-positive children had additional supratentorial lesions apart from the cerebellum, but only one of these children showed clinical signs of encephalitis. We also discussed the differential diagnosis of ADEM particularly in the latter child. Krupp et al. define signs of encephalopathy as an alteration in consciousness or behavioral changes unexplained by fever or others and designate it as a required criterion for the diagnosis of ADEM [18]. Consequently, since this child did have fever and none of the required clinical features, we included this child under the suspected diagnosis of AC. All children

were referred to us with the presumed diagnosis of AC and not ADEM because in all cases the cerebellar symptoms were leading the clinical picture.

For MOG ab testing we used serum and performed cell-based assays using full-length human MOG as recently recommended [11,19]. In assay comparison studies, the live cell-based assay performed slightly better than inactivated cell-based assays [20,21]. Protein-based enzyme-linked immunosorbent assay (ELISA) MOG-IgG tests have no clinical utility and tend to give unreliable results [11].

In addition to MOG-abs, several other abs were detected in our cohort. In one child with severe AC mGluR1 abs were present in serum and CSF. mGluR1 abs were previously reported to be present in patients with severe cerebellar syndrome that may result in cerebellar atrophy and long-term disability with around 40 % of patients with mRS>2 at the last follow-up [22,23]. mGluR1 antibodies from patients with AC were shown to be pathogenic by decreasing mGluR1 clusters in cultured neurons [23]. The authors of this study also showed that AC associated with mGluR1 abs albeit rare in children is often accompanied by other neurological symptoms such as behavioral changes, cognitive impairment or choreoathetosis. The 3-year-old boy in our cohort who was also reported in a separate study by Bien et al. also had an acute onset of cerebellar ataxia along with behavioral abnormalities [24]. The child received steroids 4 weeks after disease onset and fully recovered [24].

In two children with AC GlyR- and GFAPα-abs were found in serum. In both children a preceding respiratory tract or a documented enterovirus infection was reported. Both children had a good neurological outcome after an initial severe presentation. GlyR-abs have been described in adult and recently in pediatric patients with progressive encephalomyelitis with rigidity and myoclonus (PERM) [25]. Further data confirmed the presence of GlyR-abs exclusively in serum [26] of patients with PERM indicating that serum-GlyR-abs may be sufficient to induce the clinical manifestation.

The clinical spectrum of GFAPα-ab-positive patients may be diverse ranging from encephalitis to brainstem syndrome or transverse myelitis [27–29]. In particular in the presence of CSF GFAPα-abs patients seem to have a more severe course with widespread MRI changes (personal observation, K. Rostasy). Previous studies indicated that GFAPα-IgG positivity in serum alone is less specific and the pathogenic role in the disease process is either unclear or coexisting autoantibodies are considered as main drivers of the disease [29,30]) Nevertheless, our patient with GFAPα-abs only in serum had significant clinical improvement and decreased ab titers after steroid and rituximab therapy.

Neuropathological descriptions of children with AC are restricted to few case reports [31]. In our study we performed neuropathological analysis from one autopsy and two biopsies. All patients were negative for abs in serum and CSF. Our neuropathological studies revealed marked inflammatory infiltrates, widespread Purkinje cell loss and reactive Bergmann gliosis. Interestingly both biopsies with intense inflammation showed a strong nuclear translocation of pSTAT1 in glial cells of the cerebellar cortex. STAT1 is a member of the signal transducer and activator of transcription (STAT) family of transcription factors that transfers signals from membrane receptors to the nucleus. Multiple signals can activate phosphorylated STAT1 (pSTAT1) including proinflammatory cytokines such as IFNγ, IL6, IL2 and IL10 as well as hypoxia, viral/bacterial infections and peptide growth factors [32–34]. Further studies will be needed to elucidate the signaling pathway that may potentially serve as therapeutic target [35].

Associations of AC with various bacterial or viral pathogens such as VZV [36], Rotavirus [37], M. *pneumoniae*, or group A streptococcus [38], and others have been described.

While 14 of 36 children in our cohort had evidence of a preceding or ongoing infection, the direct pathogen influence of these detected pathogens remains unclear, especially in those children with solely high ab titers in serum. Furthermore, data regarding the serological work-up was limited based on the reported findings and did not include serological follow-up examinations on ab titers or evidence of seroconversion.

One child with an antecedent gastroenteritis was diagnosed with rotavirus-cerebellitis (see Table 1, Pat. 21) with typical clinical features such as ataxia and cerebellar mutism [37], but also signs of encephalitis and seizures [39]. However, it remains unclear whether the direct influence of the pathogen is the key factor, or whether it is much more a bystander immune response [36]. VZV represents one of the most common triggers among postinfectious AC. In our cohort, only one child (see Table 1, Pat. 31) showed evidence of VZV reactivation in a cerebellar biopsy and increased VZV-immunoglobulin G (IgG)-titers in CSF. These results were taken from the patient medical record and were only positive after some time into the disease course with a fulminant AC and initially unremarkable CSF and serum pathogen detection. The small number of VZV-positive cases in our cohort might have been a center bias, though children with VZV mostly present as postinfectious ACA and often don't show any MRI changes nor cell count elevation in the CSF and therefore, most probably rather were not eligible for the study.

The definition of AC is still controversial. Some authors request that in addition to clinical symptoms of cerebellar involvement also MRI evidence of inflammation must be present in contrast to ACA [40]. Reviewing the MRI data of our cohort, it became apparent that not all children with AC -in line with our definition-had MRI changes in the cerebellum at onset but developed MRI changes over the course of the disease. For example, one ab-negative child with parainfectious AC initially presented with recurrent vomiting and mental status changes and developed stance and gait ataxia on the following day. MRI was unremarkable initially. Due to a protracted clinical course, a second MRI was performed after one week, which now showed signs of cerebellar inflammation affecting both hemispheres. The child with the mGlur1-positive AC mentioned above also did not show cerebellar changes on MRI in the initial phase of the disease [23]. Therefore, we believe that there is an overlap between ACA and AC partly influenced by time and dynamic disease processes [40]. Children with an initially unremarkable MRI may have shown MRI changes on follow-up examinations [1] and relying on MRI evidence alone on management may run the risk of delaying treatment for patients like those in our cohort.

Our study further showed that children with a positive ab status had an overall better outcome which underlines the prognostic value of ab testing in children with AC. According to the medical records, patients were promptly treated with antiviral and antibacterial treatment in addition to steroids with similar dosages and duration. Though there were no statistically significant results comparing the treatment of both groups, we observed that in the ab-positive group, more children were treated with steroids in comparison to the ab-negative group. Also, the rate of orally given steroids was higher in the ab-positive group than in the ab-negative group. One could discuss that this higher frequency of oral steroid therapy could have led to a better outcome in the ab-positive group. Regarding intravenous steroid application, no difference could be seen in our cohort. However, the overall better outcome in the ab-positive group could also be explained as autoantibody diseases in general respond well to immunomodulatory treatment. Possibly, ab-negative cases might have underlying other causes not detectable at onset of the disease, which are doing less well under immunomodulatory treatment. Future research with standardized therapeutic protocols is needed to evaluate this clinical observation for children with AC.

Several limitations need to be addressed: First, most of the children in our cohort were analyzed only retrospectively. Secondly, ab testing was performed in three different laboratories, but all laboratories are known to be experts in the field of neuroimmunology thereby minimizing potential mistakes in the work-up of serum and CSF samples. Interestingly, our study cohort consisted of more boys than girls which was opposite to findings in another study, where slightly more girls than boys were observed [1]. Within both groups of boys and girls, there were no significant results regarding ab status and outcome data. Due to the design of the study being a multicenter study, neuroimaging methods (e.

g. field strength), patient documentation, and diagnostic procedures showed slight differences and couldn't be standardized in advance. Future prospective studies with standardized diagnostic and therapeutic procedures, as well as longer follow-up time, are needed.

The definition of AC with mandatory MRI changes at the initial event remains difficult because MRI lesions can occur over time or remain absent despite an acute cerebellar syndrome, pleocytosis, and a positive ab result.

5. Conclusion

Up to one third of children presenting with AC harbor a spectrum of autoantibodies in serum and/or CSF with the majority of them being most likely instrumental in the disease process. We recommend to include ab testing in the work-up of children with AC also in view of the therapeutic implication and observed better outcome. The detection of MOG-abs in AC does expand the MOGAD spectrum.

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Declaration of competing interest

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A. Bertolini: no.
V. Endmayr:
R. Seidl:no.
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