Long-lasting pain and somatosensory disturbances in children with myelin oligodendrocyte glycoprotein antibody-associated disease

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Title

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Running title

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Abstract

Purpose: Myelin oligodendrocyte glycoprotein antibody (MOG-Ab) is an autoantibody associated with acquired demyelinating syndrome (ADS) in childhood and adults. The pathogenic roles of MOG-Ab and long-term outcomes of children with MOG-Ab-associated disease (MOGAD) remain elusive. We investigated the clinical features of children with ADS during follow-up in our institute.

Methods: Clinical data were retrospectively analyzed using medical charts of patients managed in Kyushu University Hospital from January 1st, 2001 to March 31st, 2022. Participants were children of <18 years of age when they received a diagnosis of ADS in our hospital. Cell-based assays were used to detect MOG-Ab in serum or cerebrospinal fluid at the onset or recurrence of ADS. The clinical and neuroimaging data of MOG-Ab-positive and MOG-Ab-negative patients were statistically analyzed.

Results: Among 31 patients enrolled in this study, 22 (13 females, 59%) received tests for MOG antibodies. Thirteen cases (59%) were MOG-Ab-positive, and were therefore defined as MOGAD; 9 (41%) were MOG-Ab-negative. There were no differences between MOGAD and MOG-Ab-negative patients in age at onset, sex, diagnostic subcategories, or duration of follow-up. MOGAD patients experienced headache and/or somatosensory symptoms more frequently than MOG-Ab-negative patients (12/13 [92%] *vs.* 3/9 [22%]; p = 0.0066). Somatosensory problems included persistent pain with hyperesthesia in the left toe, perineal dysesthesia and facial hypesthesia. No specific neuroimaging findings were associated with MOGAD or the presence of somatosensory symptoms.

Conclusions: Long-lasting somatosensory disturbances are prominent comorbidities in children with MOGAD. Prospective cohorts are required to identify molecular and immunogenetic profiles associated with somatosensory problems in MOGAD.

250 words

Keywords

Myelin Oligodendrocyte Glycoprotein antibody-associated Disease; Acquired demyelinating syndrome; Pain; Somatosensory disturbance; Children

Author's summary

What is known?

Recurrence of demyelinating events occurs in a group of children with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD).

What is new?

- Long-lasting headache and somatosensory problems are frequent comorbidities with pediatric MOGAD.
- Pain and somatosensory problems may persist for more than 5 years.
- Neuroimaging data do not indicate specific findings in children with somatic disturbances.

Abbreviations

ADEM	Acute disseminated encephalomyelitis
ADS	Acquired demyelinating syndrome
CIS	Clinically isolated syndrome
IMP	Methylprednisolone-pulse
MOG	Myelin oligodendrocyte glycoprotein
MOGAD	Myelin oligodendrocyte glycoprotein-associated disease
MS	Multiple sclerosis
NMOSD	Neuromyelitis optica spectrum disorders

Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a protein expressed at the external surface of myelin, the insulating lipid layer structure of neurons in the central nervous system [1; 2]. MOG peptide is known to be an autoantigen that provokes experimental autoinflammatory encephalomyelitis (EAE) [3]. The autoantibody against MOG (MOG-Ab) is broadly detected in the central nervous system in a group of patients with acquired demyelinating syndrome (ADS) [4]. Thus, increasing efforts are being made to elucidate the pathogenic roles of MOG-Ab in each clinical category of ADS [5]. MOG-Ab-positive patients are collectively defined as patients with MOG-Ab-associated disease, MOGAD [6].

MOG-Ab is present in 34-46% of patients with ADS at <18 years of age [7], and is more frequently detected in childhood-onset acute disseminated encephalomyelitis (ADEM) than in adult ADEM [1]. Patients with MOGAD present with a various clinical features at the onset of ADS, including ADEM [8-10], optic neuritis (ON) [11], long extensive transverse myelitis (LETM) [10], and unilateral cortical encephalitis [12]. MRI typically detects disseminated T2-hyperintense lesions in the white and/or gray matter, which usually corresponds to the clinical symptoms of affected patients [13; 14]. Epstein-Barr (EB) virus is a pathogenic microbe known to be associated with the onset and recurrence of multiple sclerosis (MS) [15], whereas it remains to be determined whether EB virus infection contributes to the development of MOGAD either in children or adults [16].

The long-term prognosis of childhood-onset MOGAD has previously been considered to be generally favorable [7]. However, a certain group of children with MOGAD is now recognized to show dissemination in space and time, as observed in patients with MS [1; 17]. In fact, patients with ON are at higher risk for recurrence when MOG-Abs are persistently present [18]. It is therefore suggested that MOG-Abs play a role in the development and exacerbation of ADS [19].

Large-scale cohorts of children with ADS provide useful information about the clinical features at the onset of MOGAD and the risk of recurrence in childhood [4; 7]. To date, however, persistent symptoms of MOGAD have been less extensively studied. In the present study, we investigated whether children with MOGAD exhibit unique clinical features and treatment responses in comparison to children with MOG-Ab-negative ADS during long-term observation in our institute.

Methods

Participants

This study retrospectively enrolled pediatric patients (age <18 years) who received a diagnosis of ADS in Kyushu University Hospital from January 1, 2000 to March 31, 2022, and who fulfilled the following inclusion criteria: 1) a confirmed or suspected diagnosis of ADEM, MS, neuromyelitis optica spectrum disorders (NMOSD) or ON; 2) the first event of brain or spinal lesions suggested the mechanism of inflammatory demyelination; 3) MRI showing abnormal signals during the acute phase; and 4) the last visit to our hospital occurred in 2015 or later. Patients who received a diagnosis of primary encephalitis or myelitis [20], acute flaccid myelitis [21], traumatic injury [22], and those with unknown outcomes were excluded from the study. The diagnosis of ADS was made based on the 2013 criteria of International Pediatric Multiple Sclerosis Study Group [23] and the 2017 McDonald criteria [24-26]. NMOSD was diagnosed according to Wingerchuk's criteria [27]. Clinical data and related information were collected from the medical charts stored in Kyushu University Hospital [28]. All data were collected retrospectively using the medical charts of the participants.

Analysis of MOG-Ab

Cell-based assays (FA1156-1010-50; Euroimmun, Lübeck, Germany) were used to detect MOG-Ab in sera or cerebrospinal fluid (CSF) collected from participants at the first event of ADS, recurrence, or during the chronic phase (≥6 months after the onset) (**Table S1**) [29]. Samples were freshly prepared or safely preserved at –20°C until use. No serum or CSF samples were available for patient #2 at the initial diagnosis.

Neuroimaging

Brain and spinal lesions were evaluated immediately after the first demyelinating event, according to the standard scoring system on MRI [30]. Briefly, the number of demyelinating lesions and involved tissues were counted on 20-24 axial slices of T1, T2, fluid attenuated inversion recovery (FLAIR), diffusion-weighted, apparent diffusion coefficient (ADC) mapping data. Tissues were numbered in line with the modified Alberta Stroke Program Early CT Score (mASPECTS) [31]: 1) medulla; 2) pons and midbrain; 3, 4) cerebellum; 5, 6) optic nerves; 7, 8) cerebrum – temporal lobes; 9, 10) cerebrum - occipital lobes; 11, 12) hippocampus; 13, 14) cerebrum - frontal lobes; 15, 16) thalamus; 17, 18) basal ganglia; 19, 20) caudate nuclei; 21) corpus callosum – genu; 22) corpus callosum – splenium; and 23, 24) cerebrum – mesial, parietal and centrum ovale (**Figure S1**). Odd and even numbers represent the left and right side, respectively. Because these regions appeared in multiple slices of axial images, the MRI score could range from 0 (no lesion) to 176

(fully damaged). We evaluated the presence or absence of lesions in each slice, counted the number of lesions, and summed them up in 20-22 axial slices. The number and extension of spinal lesions were evaluated on sagittal T1- and T2-weighted images of the whole spinal cord. Three board-certified pediatric neurologists (Sonoda, Chong, and Sakai) blindly and independently evaluated MRI, discussed the evaluations, and agreed on the mean value for the final scores.

Statistics

R (https://www.R-project.org/) and JMP ver. 14 (SAS Institute, Tokyo, Japan) were used for the statistical analyses. Age, follow-up period, the number of recurrences, and MRI scores were reported as continuous values. Sex (number of female patients), ADS type at the onset (number of patients with each ADS) and treatment (number of participants who received each treatment) were presented as categorical variables. Fisher's exact test and the Wilcoxon rank sum test were applied for categorical and continuous variables, respectively. There were no missing data for variables that were included in the statistical analyses. *P* values of <0.05 were considered to indicate statistical significance.

Results

Demographic features

A total of 31 patients with ADS (17 females [55%]; median age, 8 years) were enrolled in this study (**Fig 1, Table S2**). The median follow-up period was 47 months (range: 1-198 months). Cell-based MOG-Ab assays were performed for 22 of 32 patients (69%). According to the test results, these 22 patients were considered subjects for the subsequent analysis, and were classified into the MOG-Ab-positive (MOGAD, n = 13) and seronegative (MOG-Ab-negative, n = 9) groups.

The final diagnoses of these 22 patients at the last visit to our hospital included MOGAD (n = 13; 59%), ADEM (n = 5; 23%), clinically isolated syndrome (CIS) (n = 1; 5%), MS (n = 2; 9%) and ON (n = 1; 5%) (**Fig 2, Table S3**). Two patients with NMOSD were classified into the serostatus unknown group, and were thus excluded from the 22 subjects in the subsequent analyses (**Table S2**). These 9 patients with an unknown serostatus did not differ from the 22 patients with MOGAD or MOG-Ab-negative ADS in age, sex, treatment, follow-up period, or the number of recurrences (**Table S2**). In addition, we found that two patients (22%) showed transient episodes of headache (8-year-old boy with NMOSD) and numbness of both hands (10-year-old girl) at the initial diagnosis. The frequency of patients with somatosensory problems in the excluded population was lower in comparison to the participants (22% vs. 68%, p = 0.0439, Fisher's exact test; **Table S2**).

Laboratory data

The laboratory findings at the first event of ADS are summarized in **Table S4**. There were no significant differences between the MOGAD and MOG-Ab-negative groups in the number of peripheral leukocytes, CRP, nucleated cells and total protein in cerebrospinal fluid, IgG index, or myelin basic protein levels at the onset of ADS.

Clinical profiles

All MOGAD patients and 8 (89%) of the MOG-Ab-negative patients received intravenous methylprednisolone pulse (IMP) therapy (**Table S3**). The recurrence of ADS was observed in 4 patients (31%) with MOGAD during the follow-up period (**Fig 3, Tables S2, S3**). The median number of recurrences in these patients was 6 (range: 0-9). Among them, three patients (patients #2, 3 and 5) received monthly high-dose intravenous (IVIG) and subcutaneous immunoglobulin (SCIG) therapy, which successfully extended the recurrence-free period. One of them received treatment with rituximab (patient #5). In contrast, only two MOG-Ab-negative patients (22%) had experienced a recurrence of ADS, and both were diagnosed with MS (patients #14 and #15; **Tables S2, S3**). The number of recurrences was one in patients #14 and #15. These patients continued weekly intramuscular injections of interferon-beta1a. The age at the onset, sex, and number of recurrences in MOG-Ab-negative patients were not significantly different from those in patients with MOGAD (**Tables S2, S2**).

We found that patients with MOGAD had “headache” (n = 7) and/or somatosensory problems (n = 9) during the follow-up period (**Fig 3, Table S3**). Patients with MOGAD and other diseases may frequently experience headache as a nonspecific problem. We counted this event in the present study because we could not exclude the possibility that children may express their sensory discomfort simply as “headache”. Somatosensory symptoms included left leg, toe, and palm pain with hyperesthesia (patient #2), inguinal to perineal dysesthesia (patient #3) and facial hypesthesia (patient #5). Although these somatosensory symptoms were transiently ameliorated after acute-phase treatment with IMP, they recurred and persisted over one year with or without seasonal fluctuations (**Fig 3**).

We considered the pain and discomfort to be “long-lasting” when the symptoms continued or were exaggerated after the initial treatment and when they lasted over a month. These patients did not keep records in a journal, but the parents reported their symptoms at monthly check-ups after discharge (patients #2, 3, 5, 14 and 15). The long-lasting symptoms

occurred every day during the period in which the patients suffered from them (red bars, **Fig 3**). In particular, in patient #2, the pain localized in the distal portion of the left toe had never been relieved since her first relapse at 6 years of age. While the symptom persisted for more than 5 years, it seasonally fluctuated (being worse in autumn to winter) and was exaggerated on the relapse of ADS. Acute therapy with intravenous methylprednisolone (IMP) was partially effective, whereas regular pain relievers (acetaminophen and ibuprofen) were ineffective. Monthly SCIG showed a favorable effect on extending the recurrence-free period from 15 years of age; however, it did not completely resolve the left toe pain. Transient symptoms were symptoms that were ameliorated within one month after the initial treatment (patients #1, 4, 6, 7, 8, 9 and 10).

Only two patients with MOG-Ab-negative ADS showed somatosensory problems: one with bilateral ophthalmalgia at the onset (patient #14) and another with occasional left lumbar pain (patient #15) (**Fig 3, Table S3**). Both patients received a diagnosis of MS, and their somatosensory disturbances did not continue for over 6 months. Sensory problems including headache occurred more frequently in patients with MOGAD than those with MOG-Ab-negative ADS (12/13 [92.3%] *vs.* 3/9 [33.3%], p = 0.0066, Fisher's exact test; **Table S3**). In particular, long-lasting pain and somatosensory problems were exclusively observed in patients with MOGAD, and not in those with MOG-Ab-negative ADS.

IVIG was effective for the sensory problems in patient #3 (dysesthesia of penile to perineal region). In contrast, the efficacy of IVIG and IMP was limited in patient #2 (long-lasting hypersensitivity and spontaneous pain in the left toe).

Neuroimaging features

Based on the MRI data at the initial diagnosis of ADS, we evaluated the extent of demyelinating lesions from the spinal cord to the cerebral cortex of each patient using a semi-quantitative method. We assessed the presence or absence of T2-hyperintense signals in one slice, mapped the location of each lesion to those in a reference MRI (**Fig S2**), and summed the number of lesions in 24 brain regions in each patient (**Table S5**). Because this scaling system cannot adjust for differences in the size of tissues, the number of demyelinating lesions appeared to be highest in the cerebral white matter and cortex. In contrast, relatively small regions, such as optic nerves and basal ganglia, did not show more than 3 and 10 points per patient. For example, in patient 1, 70 (67%) of 105 lesions were located in the cerebral white matter and/or cortex, whereas the optic nerves and basal ganglia showed lower scores (ON: 0 and BG: 4, **Table S5**).

Demyelinating lesions in MOGAD and MOG-Ab-negative patients involved the cerebral cortex and cerebral white matter at varying frequencies (0-85%). The total number of lesions evaluated using this scoring system was 1,086 in patients with MOGAD and 432 in patients with MOG-Ab-negative ADS. Representative lesions on brain MRI are shown in **Fig 4A**. Patients with MOGAD showed more (median 83, range: 31-116) lesions per individual than MOG-Ab-negative patients (median 47, range 1.5-100; $p = 0.0115$, Wilcoxon's rank sum test; **Fig 4B**).

The cerebral white matter and cortex were predominantly affected in patients with MOGAD and patients with MOG-Ab-negative ADS (61% and 64%, respectively). These regions were followed by the hippocampus/thalamus, spinal/brainstem, basal ganglia/caudate nuclei, cerebella, and optic nerves (**Fig 4C**). Overall, no significant difference was observed in the composition of the affected brain regions.

We performed follow-up MRI for all patients (n=22) during and after the initial treatment with IMP. In addition, for 6 patients who had relapsing events (#2, #5, #8, #13, #14 and #15), follow-up MRI was performed at each relapsing event (**Fig 3**, **Table S3**). These data were not analyzed with our MRI scoring system because the demyelinating lesions showed improvement after the acute-phase treatment, which was in agreement with the clinical recovery. Follow-up MRI was useful for evaluating the recurrence of ADS, but our quantitative measurement of brain lesions did not identify the sensory disturbance-related lesions. For example, Patient #2 showed a solitary midbrain lesion and a very faint intracortical signal in double inversion recovery (DIR) when she experienced urinary incontinence and an exacerbation of the pain localized in the left toe at 10 years of age (**Fig S2**). These lesions were less sensitively detected by conventional modalities (T1, T2, FLAIR or diffusion-weighted images). In patient #3, inguinal and perineal dysesthesia continued until we introduced IVIG. MRI did not provide evidence supporting the recurrence of ADS in the brain.

Spinal lesions were surveyed at the onset of 13 patients (100%) with MOGAD and 7 (78%) with MOG-Ab-negative ADS (**Table S5**). Thus, our scoring system did not show a difference in the frequency of spinal involvement between patients with MOGAD and those with MOG-Ab-negative ADS. No spinal lesions were detected in patient #2. However, in patient #3, weak enhancement of cauda equina was observed from the initial assessment (**Fig S3**). The enhancement of the cauda equina lasted for 4 years, and then disappeared in accordance with the improvement of sensory problems after treatment with IVIG.

Among patients who were excluded from this study, three patients showed spinal lesions that were considered to be longitudinally extensive transverse myelitis (LETM) in MOGAD, one patient exhibited confluent lesions in the cerebral white matter, basal ganglia and cerebellar peduncles, one patient had bilateral extensive ON lesions, and one patient had solid cortical lesions [13; 17; 32; 33]. Thus, these 5 patients were potentially diagnosed with MOGAD when they had received MOG-Ab tests at the onset. Two patients showed spinal, brainstem and ON lesions that supported the diagnosis of NMOSD [27; 34].

Discussion

In this study, we analyzed the clinical courses of 13 children with MOGAD in comparison to patients with MOG-Ab-negative ADS. Patients with MOGAD developed headache and/or somatosensory disturbances more frequently than those with MOG-Ab-negative ADS at the onset of disease. These symptoms favorably responded to acute-phase treatment with IMP therapy; however, 3 patients with MOGAD experienced somatosensory symptoms that persisted for more than 6 months. However, no clinical features, laboratory findings or neuroimaging data predicted long-lasting symptoms in MOGAD.

Various forms of somatosensory disturbance are known to be associated with transverse myelitis and MOGAD [7; 35]. These include both positive (pain, hyperesthesia and dysesthesia) and negative symptoms (hypesthesia and anesthesia). Somatosensory problems fluctuate not only with other neurological signs at the onset or recurrence of ADS, but also with psychosocial settings in adult patients with MOGAD [4]. Nociceptive or neuropathic pain is well-defined and has received attention in clinical studies on adult patients with MS and MOGAD [4; 36; 37]. In fact, adult patients suffer from persistent pain and inexpressible discomfort that may respond poorly to steroids and other palliative therapies [38]. Although somatosensory problems affect the sleep-wake cycle, interests and social activities, including school attendance, these topics have been less extensively discussed as a crucial matter of children with MOGAD in comparison to adults [39]. One of the reasons might be related to the lack of objective, biological parameters to measure the degree of dysfunction in the somatosensory system. Thus, physicians rely largely on questionnaire-based algometry, such as the McGill Pain Questionnaire [4]. In children, however, chronic pain and sensory distress were difficult to discriminate from hypersensitive phenotypes in somatoform disorder, autism and other forms of neurodevelopmental disorders. Knowing that seasonal oscillation of pain in the left toe was apparent in one of our patients, this study noted the value of

longitudinal observation in addressing the issues that children with MOGAD may bear for years after the onset.

From a pathophysiological perspective, circulating MOG-Abs may directly or indirectly induce inflammatory responses in any of the ascending neurons from the peripheral nerves to those innervating the primary somatosensory cortex [40]. Thus, fine neuronal inflammation might be present at an undetectable level, contributing to the excessive or insufficient activation of neurons in the sensory system [41-43]. Why somatosensory symptoms were not correlated with the extent of grossly detectable lesions on brain MRI remains unknown. Notably, however, DIR identified fine cortical lesions in patient #2, suggesting that it might be a useful modality for showing demyelinating lesions in the cerebral cortices of patients with MOGAD. Future studies may clarify whether DIR serves as an alternative method for the quantitative measurement of cortical lesions in patients with MOGAD who show long-lasting sensory problems.

In this study, spinal or brainstem lesions were not associated with somatosensory problems. However, sensory symptoms are commonly observed in patients with transverse myelitis [44]. Thus, DIR or more suitable MRI modalities may identify specific lesions at the spinal or brainstem level in patients with such long-lasting sensory phenotypes. Favorable responses to IMP and IVIG suggest that the sensory problems result from the persistently active inflammation in variable levels of sensory circuits, as is frequently observed in patients with chronic inflammatory demyelinating polyneuropathy [45]. In fact, an overlapping, central-and-peripheral nervous system syndrome has been recently proposed as a pathomechanism of somatosensory deficits in a group of patients with MOGAD [46]. From this perspective, the evaluation of autoantibodies (anti-neurofascin 155, contactin-associated protein 2 or GM1) may be warranted due to the difficulty in detecting neuroimaging-negative somatosensory symptoms in our patients.

Two patients with NMOSD were classified into the serostatus unknown group, and they showed irreversible visual impairments. Nevertheless, they did not have any other somatosensory symptoms. Although we cannot generalize the clinical features of NMOSD from these two patients alone, it may reflect that aquaporin 4 (AQP4)-Ab-positive NMOSD has distinct mechanisms from MOGAD [47]. Indeed, patients with MOG-Ab-positive NMOSD more frequently showed involvement of the conus in the spinal cord and deep gray nuclei in the brain in comparison to patients with AQP4-Ab-positive NMOSD [48]. More recently, patients with MOGAD have been reported to develop combined central and

peripheral demyelination syndromes and sensory polyradiculoneuropathy [1; 46]. Taken together, MOGAD may affect a broader range of neurons, causing various types of neuroinflammatory lesions, in comparison to AQP4-Ab-positive NMOSD and seronegative ADS.

Therapeutic standards remain to be established for somatosensory disturbances in children with MOGAD. Previous reports showed palliative effects of corticosteroids, pregabalin, and gabapentin in adults with MOGAD and MS [49; 50]. Twenty-one patients (95%) in this study received IMP therapy as an acute-phase treatment, which proved partially effective for reducing somatosensory symptoms. However, the symptoms did not disappear after the acute-phase treatment in three patients (patients #2, 3 and 5). Novel therapeutic targets might be identified through the constitutive analysis of cytokine levels in the cerebrospinal fluid [51], oxidized phospholipids or prostaglandins [52; 53], single-cell molecular profiling of microglia [54]. Further efforts, using either animal or other experimental models, are required to delineate immunological factors that determine susceptibility to the somatosensory disturbances in patients with MOGAD [55].

The present study was associated with some limitations. First, this was a retrospective, single-institute study. For this reason, we excluded 9 patients (29%) whose MOG-Ab test results were unknown from the analysis. We collected clinical data of participants from 2001 to 2022. The study population is therefore considered heterogeneous in terms of the clinical setting. For example, the availability of MOG-Ab tests has remarkably changed in recent years. Thus, in future prospective cohorts, cell-based MOG-Ab assays need to be performed throughout the study period for all patients with ADS, regardless of the presence or absence of somatosensory symptoms. The assessment of somatosensory disturbances may require agreement among caregivers, patients and parents on the basis of a consistent scaling system throughout the observation period. Second, this study did not yield electrophysiological data that would support the somatosensory symptoms in children with MOGAD. It is not always feasible to perform this type of study for children with pain and hypersensitivity; however, the measurement of somatosensory evoked potentials may provide useful insight into the location of MRI-negative inflammatory damage in ascending neurons [43]. The status of EB virus infection remained unknown in this study [15]. This is an important issue for childhood-onset ADS that should be addressed in future prospective cohorts. Lastly, we were unable to serially test the MOG-Ab titer during the follow-up period in one patient. The chronological association of somatosensory symptoms with the MOG-Ab titers may provide further information about the disease activity for patients without explainable lesions on MRI. From this viewpoint,

more convenient and quantitative methods are considered to be necessary to detect the MOG-Ab in circulating blood [56].

Conclusion

This study clarifies that children with MOGAD more frequently present with somatosensory disturbances at and after the onset than was previously recognized. These symptoms are hard to assess with currently available standards for neurological impairments. We propose that somatosensory disturbances are one of cardinal problems that should be overcome in the long-term management of MOGAD in childhood.

Supplementary data

Fig S1. MRI scoring system in this study
Fig S2. A midbrain lesion detected by double inversion recovery in patient #2
Fig S3. Gadolinium enhancement of the cauda equina in patient #3.
Table S1. Timepoints, methods, and results of MOG-Ab tests
Table S2. Demographics of 22 subjects and 9 patients with unknown serostatus
Table S3. The diagnosis, clinical signs and MOG-Ab status of patients in the present study
Table S4. Summary of laboratory test results
Table S5. Summary of neuroimaging features

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Statements and Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics statement

This study was conducted in compliance with our institutional guidelines for clinical studies. Research protocol was approved by the institutional review board at Kyushu University (21046-00). For the presentation of cases, written informed consent was obtained from the parents.

Author contributions

All authors read and approved the final manuscript. Yuko Ichimiya: Data collection, formal analysis, original draft preparation; Pin Fee Chong: Reviewing and editing, funding acquisition. Yuri Sonoda: Data curation, investigation; Vlad Tocan: Investigation, reviewing and editing; Toshiyuki Takahashi: Investigation; Mitsuru Watanabe: Validation; Hiroyuki Torisu: Data collection, reviewing and editing; Ryutaro Kira: Data collection, reviewing and editing; Noriko Isobe: Supervision, Reviewing and editing, funding acquisition; Junichi Kira: Supervision, Reviewing and editing; Yasunari Sakai: Conceptualization, original draft preparation, reviewing and editing; Shouichi Ohga: Conceptualization, funding acquisition, reviewing and editing.

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Figure legends

Figure 1. A selection flowchart for eligible subjects in this study

Patients were searched on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) in our hospital. Among 108 patients, 31 met the inclusion criteria (age <18 years and a diagnosis of acquired demyelinating syndrome [ADS]). Twenty-two received cell-based tests for MOG-Ab (positive, n = 13; negative, n = 9). Nine patients with unknown serostatus were removed from the analysis. ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; ON, optic neuritis; MS, multiple sclerosis; Ab, antibody; +, positive; -, negative.

Figure 2. Age, sex, diagnosis, and the follow-up periods of patients with MOGAD and MOG-Ab-negative results

Age at the onset (vertical scale) and the duration of follow-up (horizontal scale) are shown for 13 patients with MOGAD (left) and 9 patients with MOG-Ab-negative results. Color codes indicate the diagnostic categories of patients with acquired demyelinating syndromes (ADS).

Ab, antibody; ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; MS, multiple sclerosis; ON, optic neuritis.

Figure 3. Somatosensory disturbances in the clinical course of the 22 patients

The presence and duration of somatosensory disturbances (red) are shown for each patient. The types of ADS (ADEM, CIS, ON) at the disease onset are indicated by color.

Figure 4. Neuroimaging features of childhood-onset ADS and MOGAD

(A) Axial slices of fluid-attenuated inversion recovery (FLAIR). Patients with MOGAD (#1 to 13) and those with MOG-Ab-negative results (#14 to 22) showed variable degrees of T2-hyperintense lesions. Red font indicates patients with somatosensory disturbances.

(B) Violin-dot plots show the MRI scores of patients with MOGAD and MOG-Ab-negative results. Red circles denote the patients with somatosensory disturbances. *P<0.05 (Wilcoxon's rank sum test).

(C) Pie charts indicate the composition (%) of affected brain regions in patients with MOGAD and those with MOG-Ab-negative results. CTX/WM, cerebral cortex and white matter; HP/TH, hippocampus and thalamus; SP/BS, spinal cord and brainstem; BG/CN, basal ganglia and caudate nucleus; CB, cerebellum; and ON, optic nerve.

Table S1. Timepoints, methods and results of MOG-antibody tests for the present cases

ID	Age at onset (year)	Diagnosis	MOG-Ab test† (Years or months after the onset, Method-sample, Titer)			
			1st	2nd	3rd	4th
1	2.5	MOGAD	Onset, CBA-serum, 512			
2	4.1	MOGAD	4 years, CBA-serum, 128 4 years, CBA-CSF, 32	5 years, CBA-serum, negative		
3	6.0	MOGAD	Onset, CBA-serum, 1024	4 months, CBA-serum, 128	42 months, CBA-serum, 128	47 month, CBA-serum, negative
4	7.3	MOGAD	Onset, CBA-serum,128			
5	7.6	MOGAD	Onset, CBA-serum,1024	14 months, CBA-serum, 2048		
6	9.1	MOGAD	Onset, CBA-serum, 4096			
7	10.8	MOGAD	Onset, CBA-serum, 256	30 months, CBA-serum, negative		
8	13.8	MOGAD	Onset, CBA-serum, 8192	1 month, CBA-serum, 8192	10 months, CBA-serum, 8192	26 months, CBA-serum, 4096
9	11.7	MOGAD	Onset, CBA-serum, 128			
10	1.7	MOGAD	Onset, CBA-serum, 2048			
11	8.8	MOGAD	Onset, CB-serum, Y			
12	12.3	MOGAD	Onset, CB-serum, Y			
13	13.2	MOGAD	Onset, CBA-serum, 128 Onset, CBA-CSF, 4	3 months, CBA-serum,128 3 months, CBA-CSF, 4		
14	7.5	MS	Onset, CB-serum, -			
15	9.3	MS	Onset, CB-serum, -			
16	0.6	CIS	Onset, CB-serum, -			
17	1.3	ADEM	Onset, CB-serum, -			
18	3.2	CIS	Onset, CB-serum, -			
19	4.4	ADEM	Onset, CB-serum, -			
20	5.6	ADEM	Onset, CB-serum, -			
21	10.3	ADEM	Onset, CB-serum, -			
22	15.0	ON	Onset, CB-serum, -			

†CB = cell-based binary test (commercially provided); CBA = cell-based semiquantitative assay. Data represent Y (yes, present) and - (absent) in CB tests.
Ab = antibody; ADEM = acute disseminated encephalomyelitis; CIS = clinically isolated syndrome; MOGAD = MOG-Ab-associated disorder; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; and ON = optic neuritis.

Table S2. Demographics of 22 subjects and 9 patients with unknown serostatus

	Participants, n = 22		Serostatus unknown (excluded) n = 9	P-value Participants *vs.* excluded
	MOGAD n = 13	MOG-Ab negative n = 9		
Age at onset, median year [range]	8 [1.7-13.8] †	5 [0.6-15.0]	8 [0.6-16.7]	0.257 ‡
Female (%)	9 (69)	4 (44)	4 (44)	0.693 §
ADS type at onset				
ADEM (%)	5 (38)	5 (56)	2 (22)	0.418 §
CIS (%)	5 (38)	2 (22)	5 (55)	0.253 §
ON (%)	3 (23)	2 (22)	0 (0)	0.286 §
NMOSD (%)	0 (0)	0 (0)	2 (22)	0.077 §
Treatment				
IMP (%)	13 (100)	8 (89)	9 (100)	1.0 §
IVIG (%)	7 (54)	2 (22)	1 (11)	0.205 §
PE (%)	3 (23)	0 (0)	2 (22)	0.613 §
DMT (%)	3 (23)	2 (22)	2 (22)	1.0 §
Follow-up period, median months [range]	44 [5-134]	69 [5-167]	63 [1-198]	0.500 ‡
Number of recurrences, median [range]	6 [0-9]	1 [0-2]	6 [0-9]	0.843 ‡
Sensory problems (%)	12 (92)	3 (33)	2 (22)	0.0439 §

† Age represents years; ‡ Wilcoxon's rank sum test; and § Fisher's exact test

Ab = antibody, ADEM = acute disseminated encephalomyelitis, MS = multiple sclerosis, CIS = clinically isolated syndrome, ON = optic neuritis, NMOSD = neuromyelitis optica spectrum disorder, MOGAD = MOG-Ab-associated disorder, IMP = intravenous methylprednisolone pulse, IVIG = intravenous immunoglobulin, PE= plasma exchange, DMT = disease-modifying therapy

Table S3. The diagnosis, clinical signs and MOG-Ab status of patients in the present study

ID	Age at onset†	Sex	Diagnosis		Prodromal sign	Sensory problems		Follow-up (months)	Presence or absence of MOG Ab‡			Treatment	Relapse, Type of ADS
			Onset	Last visit		Headache	Somatosensory		Onset	Peak	Last		
1	2.5	M	CIS	MOGAD	Gait disturbance	-	Systemic pain	5	512	512 (onset)	NA	IMP, IVIG	0
2	4.1	F	ADEM	MOGAD	Seizure	Y	Dysesthesia of tongue	134	Not tested	128 (84 mo)	Negative	IMP, SCIG	6 MS
3	6.0	M	ADEM	MOGAD	Fever, coma	Y	Dysesthesia of penile to perineal region	55	1024	1024 (onset)	Negative	IMP, IVIG	0
4	7.3	F	ADEM	MOGAD	Fever, coma	Y	Chest pain	35	1024	1024 (onset)	Negative	IMP, IVIG, PE	0
5	7.6	M	CIS	MOGAD	Fever	Y	Hypesthesia, Headache	92	1024	2048 (12 mo)	128	IMP, IFN, DMT, SCIG, RTX	9 r-ADEM
6	9.1	F	ON	MOGAD	Visual impairment	-	Ophthalmalgia	75	4096	4096 (onset)	Negative	IMP	0
7	10.8	F	CIS	MOGAD	Visual impairment	-	Dysesthesia	44	256	256 (onset)	Negative	IMP	0
8	13.8	F	CIS	MOGAD	Visual impairment	-	Hypesthesia	36	8192	8192 (onset)	4096	IMP, IVIG, PE, DMT	5 r-ON
9	11.7	F	ON	MOGAD	Visual impairment	-	Ophthalmalgia, Dysesthesia	47	128	128 (onset)	NA	IMP	0
10	1.7	F	ADEM	MOGAD	Seizure	-	-	24	2048	2048 (onset)	NA	IMP, IVIG	0
11	8.8	F	ON	MOGAD	Visual impairment	Y	-	3	Y	NA	NA	IMP	0
12	12.3	F	ADEM	MOGAD	Coma	Y	-	49	Y	NA	NA	IMP, IVIG	0
13	13.2	M	CIS	MOGAD	Visual impairment	Y	-	20	128	128 (1 mo)	128 (3 mo)	IMP, IVIG, PE	3 r-ADEM
14	7.5	M	ON	MS	Visual impairment	Y	Ophthalmalgia	105		-		IMP, IFN	1 r-ON
15	9.3	F	CIS	MS	Paralysis	Y	Dysesthesia	167		-		IMP, IFN	1 MS
16	0.6	M	ADEM	ADEM	Paralysis	-	-	69		-		IMP	0
17	1.3	F	ADEM	ADEM	Fever, coma	-	-	13		-		IMP	0
18	3.2	F	CIS	CIS	Paralysis	-	-	34		-		IMP, IVIG	0
19	4.4	M	ADEM	ADEM	Fever, Seizure	Y	-	71		-		IMP, IVIG	0
20	5.6	F	ADEM	ADEM	Fever, Seizure	-	-	91		-		-	0
21	10.3	M	ADEM	ADEM	Fever, coma	-	-	46		-		IMP	0
22	15.0	M	ON	ON	Visual impairment	-	-	5		-		IMP	0

†years; ‡Y, yes (present) or MOG Ab-positive; -, absent or MOG Ab-negative; NA, not available

Ab = antibody; ADEM = acute disseminated encephalomyelitis; CIS = clinically isolated syndrome; DMT = disease-modifying therapy; IFN = interferon-β1; IMP = intravenous methylprednisolone pulse; IVIG = intravenous immunoglobulin; MOGAD = MOG-Ab-associated disorder; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis; PE = plasma exchange; r-ADEM/ON = recurrent ADEM/ON; RTX = rituximab; SCIG = subcutaneous infusion of immunoglobulin.

Table S4. Summary of laboratory test results

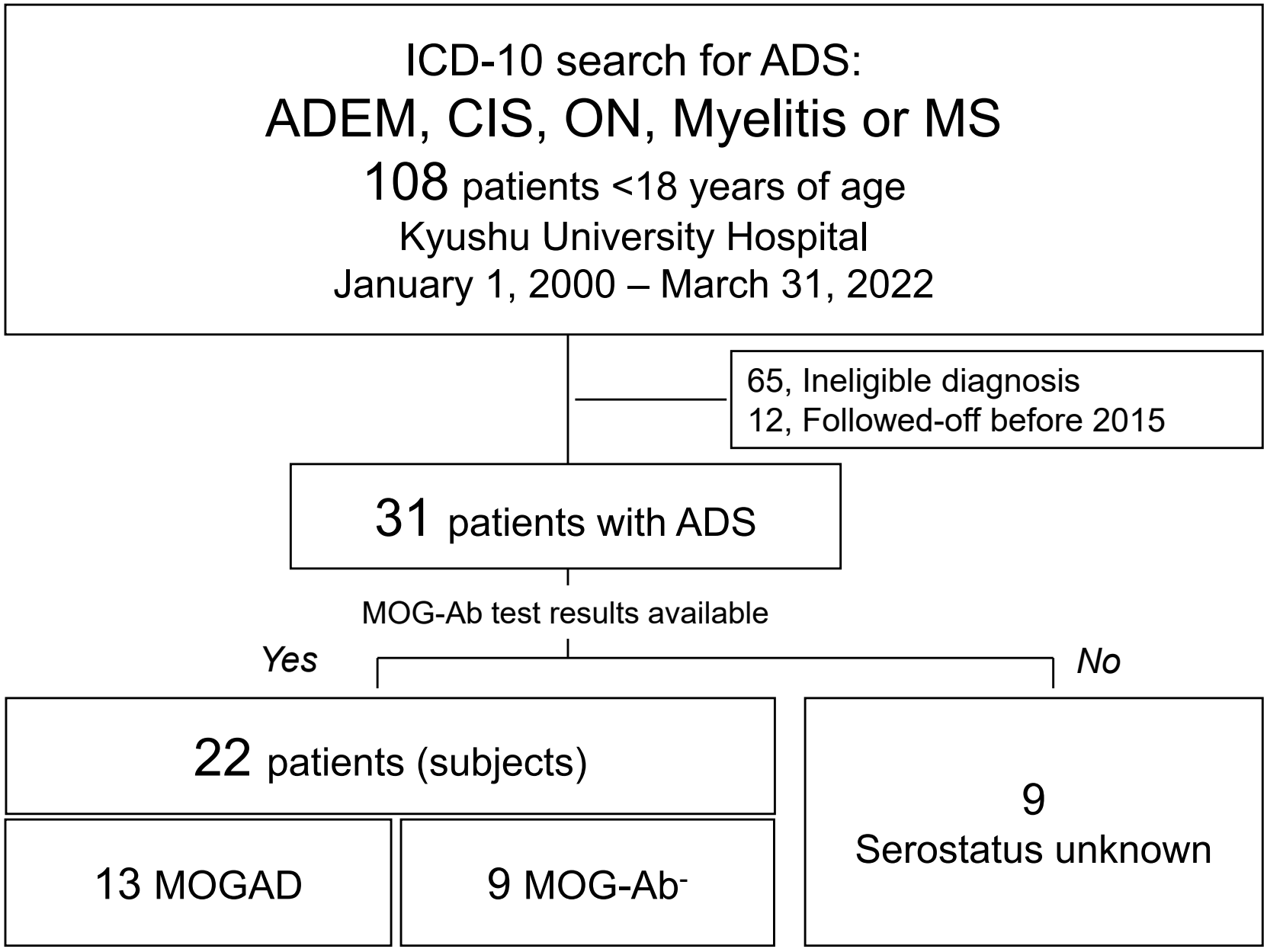
ID	Age at onset, year	Diagnosis	Blood test		Cerebrospinal fluid			
			Leukocyte, μl (Neutrophil, %)	C-reactive protein, mg/dl	Cell count, μl	Protein, mg/dl	IgG index	MBP, ng/ml
1	2.5	MOGAD	10540	0.07	17	26	0.62	352
2	4.1	MOGAD	17380	0.84	22	9	0.51	352
3	6.0	MOGAD	6720	0.35	10	24	0.26	< 31.3
4	7.3	MOGAD	16120	0.33	410	366	0.77	275
5	7.6	MOGAD	16400	0.38	17	27	NA	7010
6	9.1	MOGAD	13630	0.09	4	19	0.53	130
7	10.8	MOGAD	5700	0.01	10	39	0.42	40
8	13.8	MOGAD	7090	0.01	0	32.5	0.62	<40
9	11.7	MOGAD	10210	0.01	10	57	0.64	< 31.3
10	1.7	MOGAD	15810	0.28	6	15	0.69	1750
11	8.8	MOGAD	6820	0.07	NA	NA	NA	571
12	12.3	MOGAD	6580	0.03	35	70	0.62	1750
13	13.2	MOGAD	7150	0.02	17	47	0.67	60.1
14	7.5	MS	10060	0.10	31	28	0.43	56.6
15	9.3	MS	9180	0.01	2	15	0.5	405
16	0.6	CIS	16670	0.03	5	51	0.56	450
17	1.3	ADEM	2230	0.24	2	23	0.88	436
18	3.2	CIS	11210	0.63	1	20	0.5	< 31.3
19	4.4	ADEM	18420	0.08	6	17	NA	932
20	5.6	ADEM	4150	0.72	1	9	NA	NA
21	10.3	ADEM	6040	0.01	10	48	0.29	< 31.3
22	15.0	ON	6130	0.01	6	27	0.46	< 31.3

MBP = myelin basic protein, NA = not available

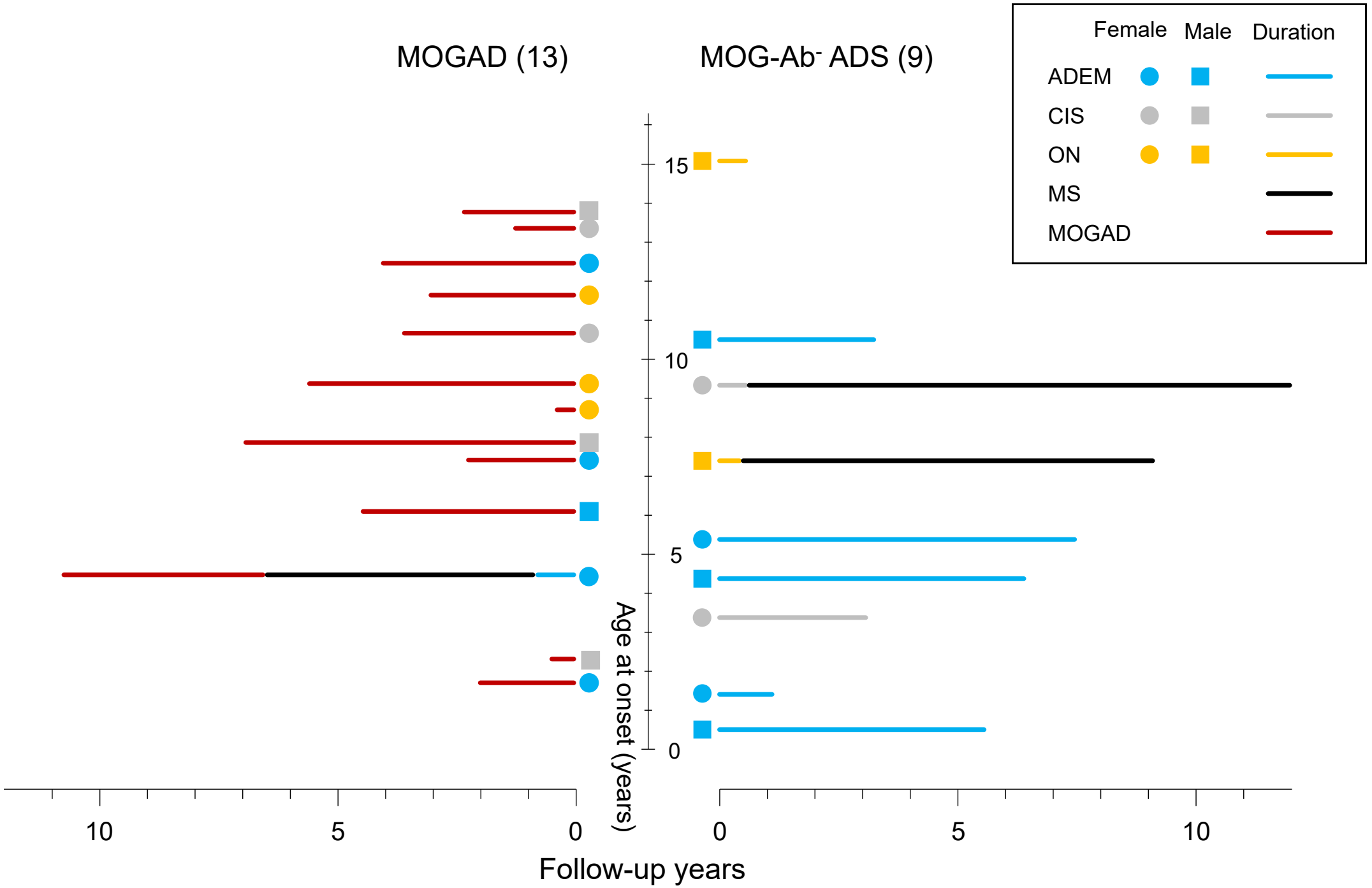
Table S5. Summary of neuroimaging features

ID	BS		CB		HIP+TH						ON		BG		CTX										Sum
	ROI																								
	1	2	3	4	11	12	15	16	19	20	5	6	17	18	7	8	9	10	13	14	21	22	23	24	
1	2	7	4	4	2	2	3	3	2	2			2	2	13	13	7	7	11	11			4	4	105
2	2	3	3	4	2	2	2	2					2	2	8	8	3	3	2	4				1	53
3	2	6	2	2	2	2	3	3	3	3			5	5	13	13	8	8	9	9			3	3	104
4	2	6	3	4	4	4	4	4	4	4	1	1	5	5	13	13	8	8	10	10			3	3	119
5	2	8	3	3	3	3	3	3			1	1			8	10	9	10	8	6			6	5	92
6	1	5			2	2	3	3					2	2	6	6	8	8	7	7					62
7	2	5	2	2	1	1	2	2			2		2	2	5	5	4	4	5	4			3	2	55
8	2	9	3	3	2	2	3	3				1			7	7	9	9	7	7			1	1	76
9	2	8	4	4	3	3	3	3		1	1	2		1	9	10	7	7	9	11			2	1	91
10	2	7	1	1	1	2	3	3	1				1	3	13	13	12	12	12	12			4	4	107
11	2	6	2	2	1	1	3	3		1		1		1	1	3		3							30
12	2	7	7	7	4	4	3	3	4	4	1	1	4	4	9	9	5	3	5	8			1	1	96
13	2	5	4	4	3	3	3	3		2	1	1		2	11	11	8	8	10	9			3	3	96
14		5	1	1			2	2			1	2		1	4	4			2	2					27
15	2	8	4	4	3	3	3	3	2	2			4	4	13	13	6	6	9	9					98
16		1																							1
17	1	1	2	2			1	1							3	3	9	9	8	8			2	2	52
18	2	3	2	2																					9
19	1	4	2	2			3	3	3	4			2	2	13	13	9	9	12	12			5	5	104
20	1		1	1			2	2			1		1	1	8	8	5	5	4	4		2			46
21	2	2	2	2			3	3	1	1			4	4	10	5	9	9	9	5				1	72
22	2	6	1	1			3	3				1	2	2	1	1									23

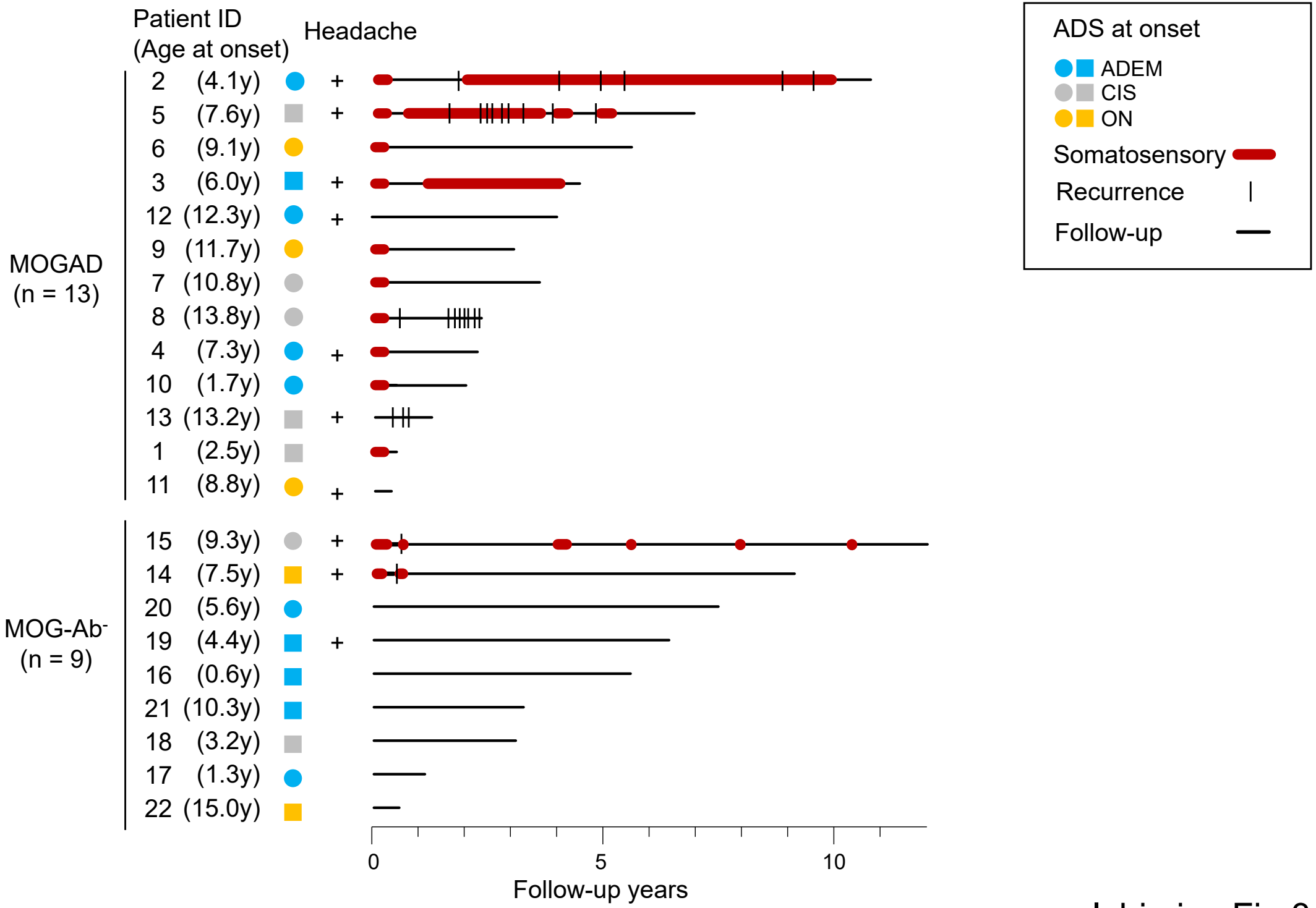
BG = basal ganglia (+caudate nuclei); CB = cerebellum; CTX = cerebral cortex and white matter; HIP/TH = hippocampus/thalamus; ON = optic nerve; BS = brainstem; and ROI = region of interest



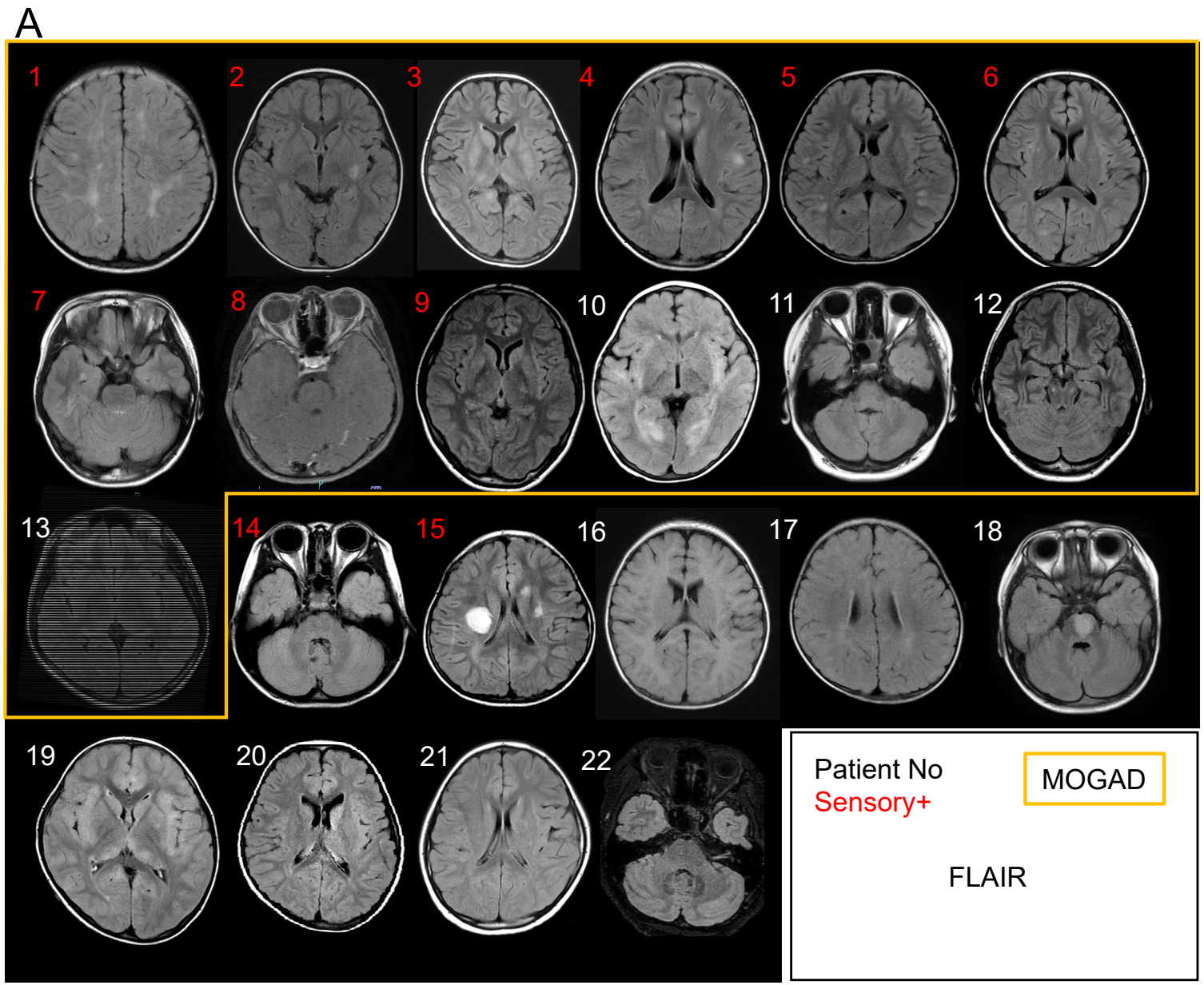
Ichimiya Fig 1

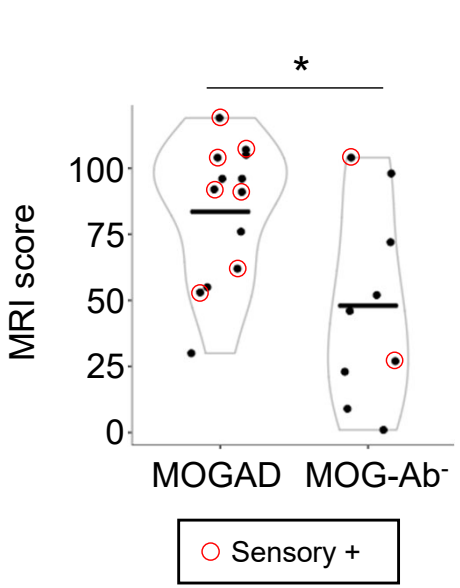


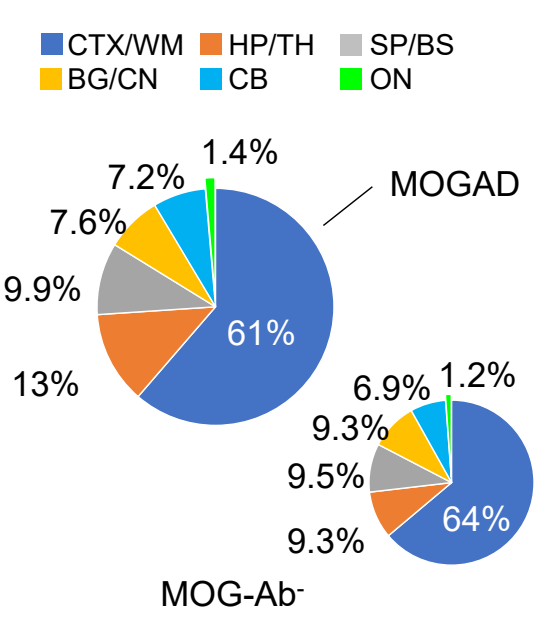
Ichimiya Fig 2



Ichimiya Fig 3







Ichimiya Fig 4