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Association of Progressive Cerebellar Atrophy With Long-term Outcome in Patients With Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

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Abstract

IMPORTANCE—Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disorder that occurs with IgG antibodies against the GluN1 subunit of NMDAR. Some patients develop reversible diffuse cerebral atrophy (DCA), but the long-term clinical significance of progressive brain and cerebellar atrophy is unknown.

OBJECTIVE—To report the long-term clinical implications of DCA and cerebellar atrophy in anti-NMDAR encephalitis.

DESIGN, SETTING, AND PARTICIPANTS—A retrospective observational study and long-term imaging investigation was conducted in the Department of Neurology at Kitasato University. Fifteen patients with anti-NMDAR encephalitis admitted to Kitasato University Hospital between

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Author Contributions: Dr Iizuka had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Iizuka, Dalmau.

Acquisition, analysis, or interpretation of data: All authors.

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January 1, 1999, and December 31, 2014, were included; data analysis was conducted between July 15, 2015, and January 18, 2016.

EXPOSURES—Neurologic examination, immunotherapy, and magnetic resonance imaging (MRI) studies were performed.

MAIN OUTCOMES AND MEASURES—Long-term MRI changes in association with disease severity, serious complications (eg, pulmonary embolism, septic shock, and rhabdomyolysis), treatment, and outcome.

RESULTS—The clinical outcome of 15 patients (median age, 21 years, [range, 14–46 years]; 10 [67%] female) was evaluated after a median follow-up of 68 months (range, 10–179 months). Thirteen patients (87%) received first-line immunotherapy (intravenous high-dose methylprednisolone, intravenous immunoglobulin, and plasma exchange alone or combined), and 4 individuals (27%) also received cyclophosphamide; 2 patients (13%) did not receive immunotherapy. In 5 patients (33%). ovarian teratoma was found and removed. Serious complications developed in 4 patients (27%). Follow-up MRI revealed DCA in 5 patients (33%) that, in 2 individuals (13%), was associated with progressive cerebellar atrophy. Long-term outcome was good in 13 patients (87%) and poor in the other 2 individuals (13%). Although cerebellar atrophy was associated with poor long-term outcome (2 of 2 vs 0 of 13 patients; $P = .01$), other features, such as DCA without cerebellar atrophy, serious complications, ventilatory support, or prolonged hospitalization, were not associated with a poor outcome. Five patients with DCA had longer hospitalizations (11.1 vs 2.4 months; $P = .002$), required ventilatory support more frequently (5 of 5 vs 4 of 10 patients; $P = .04$), and developed more serious complications (4 of 5 vs 0 of 10 patients; $P = .004$) compared with those without DCA. Although DCA was reversible, cerebellar atrophy was irreversible.

CONCLUSIONS AND RELEVANCE—In anti-NMDAR encephalitis, DCA can be reversible and does not imply a poor clinical outcome. In contrast, cerebellar atrophy was irreversible and associated with a poor outcome. This observation deserves further study to confirm progressive cerebellar atrophy as a prognostic marker of poor outcome.

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an antibody-mediated disorder characterized by prominent psychiatric symptoms and followed by a decreased level of consciousness with hypoventilation, dyskinesias, seizures, and autonomic symptoms.[1–4] These symptoms are caused mainly by internalization of the NMDAR without complement activation.[2,5] Despite severe symptoms or prolonged coma, 81% of the patients show substantial recovery at 24 months, but the remaining patients still have severe disability, with an estimated mortality of 7% at 24 months.[4] Second-line immunotherapies (cyclophosphamide, rituximab) have been recommended in refractory cases,[4] but up to 20% of the patients may be resistant to the currently available medications.[4] Indicators of poor outcome include delayed initiation of immunotherapy and requirement of intensive care support[4]; however, to our knowledge, the association between long-term outcome and brain atrophy has not been assessed.

In neurodegenerative disorders or classic paraneoplastic neurologic syndromes, brain atrophy is usually considered irreversible. In patients with a persistent unresponsive state associated with brain atrophy, discontinuation of supportive care may be considered.

However, a good long-term outcome was reported[6] in 4 patients with anti-NMDAR encephalitis who recovered gradually over 4 to 5 years despite the presence of marked brain atrophy in 2 of these individuals, which surprisingly became reversible.[7] Since then, we evaluated an additional patient with reversible brain atrophy and 2 patients who developed persistent disability associated with cerebellar atrophy. We realized that little attention has been focused on cerebellar atrophy. The aim of this study was to determine a possible association between cerebellar atrophy and poor long-term outcome.

Methods

Patients

We retrospectively reviewed clinical information on 15 patients with anti-NMDAR encephalitis who were admitted to Kitasato University Hospital between January 1, 1999, and December 31, 2014. Oral informed consent was obtained from patients or their family. Studies were approved by institutional review boards of Kitasato University and the review board of Hospital Clínic, University of Barcelona.

Clinical features of 6 patients (2–6 and 8) have been reported previously,[6–9] and detailed clinical information on the remaining 9 patients is described in eAppendix in the Supplement. Information on symptoms, electroencephalograms, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), treatments, complications, and outcomes was obtained by us or referring physicians. In the first 5 patients (1–5), who presented 4 to 8 years before the 2007 discovery of NMDAR antibodies,[1] the diagnosis of anti-NMDAR encephalitis was confirmed using archived serum and CSF obtained by the time of disease presentation. Three patients (7, 9, and 14) were initially admitted to a different hospital and treated for 8 to 18 months before they were transferred to our hospital (the intervals between presentation and referral were 8, 12, and 48 months, respectively).

The diagnosis of anti-NMDAR encephalitis was made based on clinical symptoms and signs, CSF analysis, electroencephalogram, brain MRI, and detection of NMDAR antibodies.[1] Chronological MRI changes in association with disease severity, serious systemic complications, treatments, and long-term outcome were evaluated.

MRI Studies

Brain MRIs were retrospectively reviewed, but they were not intended to measure the cerebral volume, and long-term follow-up did not allow us to use the same MRI equipment. Therefore, chronological changes were visually assessed based on T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images obtained with a 1.5-T (3.0-T for additional studies) clinical scanner (Signa HDxt; GE Healthcare). Initial MRIs at presentation, including those obtained at referring hospitals, were used as baseline to assess subsequent changes that were visually classified into 3 groups: (1) no brain atrophy, (2) diffuse cerebral atrophy (DCA), and (3) cerebellar atrophy.

Treatments, Systemic Complications, and Long-term Outcome

The treatment strategy was decided by patients' physicians and differed depending on the time of presentation: either before or after knowledge of this disease among physicians. Although anti-NMDAR encephalitis was first reported in January 2007,[1] this disorder was not well recognized in Japan until late 2007 to early 2008.[6] With a few exceptions,[10] most patients identified before 2011 (prior to publication of a treatment algorithm[3]) remained undertreated.

Treatments were classified as (1) symptomatic (eg, antiepileptic agents, sedative drugs), (2) first-line immunotherapies (intravenous high-dose methylprednisolone, 1000 mg/d for 3–5 days; intravenous immunoglobulin, 0.4 g/kg/d for 5 days; and plasma exchange alone or combined), (3) second-line immunotherapies (intravenous cyclophosphamide, 500 mg/m^2 monthly for 1–6 cycles), (4) long-term oral immunotherapy (prednisone, azathioprine, or tacrolimus), and (5) tumor resection. Treatment with rituximab was not used.

Time from onset of central nervous system symptoms to immunotherapy was determined in each case; however, in patients 8 and 14, the symptom onset at relapse was used to estimate the time to immunotherapy because both individuals presented as having typical anti-NMDAR encephalitis at relapse. In one of these patients, the first episode was isolated seizures; in the other individual, isolated psychiatric symptoms occurred first, with both symptoms improving without immunotherapy. Patients 2 and 3 improved without immunotherapy; therefore, the time was not determined.[6]

Hospitalization was defined as the time in the hospital required for treatment until transfer to a rehabilitation facility or home. Pulmonary embolism, serious deep vein thrombosis involving the inferior vena cava or requiring an inferior vena cava filter, septic shock, rhabdomyolysis, multiple organ dysfunction syndrome, disseminated intravascular coagulation, arterial thrombosis, and transient cardiac arrest were considered as serious systemic complications; asymptomatic deep vein thrombosis was not considered a serious complication.

Neurologic disability at the last follow-up was evaluated by the modified Rankin Scale (mRS).[11] Good outcome was defined as an mRS score of 0 to 2 at the last follow-up, and poor outcome was defined as an mRS score of 3 or higher. We assessed potential factors that might affect long-term outcome or brain atrophy, including sex, age at disease onset, requirement of mechanical ventilatory support or duration of ventilatory support, serious complications, time from symptom onset to immunotherapy, presence of tumor, first-line immunotherapy, second-line immunotherapy, long-term immunosuppressants, hospitalization, and observational periods.

Antibody Assays

Serum or CSF obtained at presentation was kept frozen until antibody assay, which was performed using immunohistochemistry with frozen sections of rat brain and cell-based assay as previously reported.[1] In patient 7, antibodies were examined using samples obtained 8 months after symptoms developed (eTable in the Supplement). Additional antibodies against other neuronal cell surface and synaptic proteins (AMPAR [alpha-

amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor], γ-aminobutyric acid-A receptor, γ-aminobutyric acid-B receptor, contactin-associated protein-like 2, and leucine-rich glioma inactivated-1) were also measured in serum or CSF by cell-based assay.[12–16] Antibody testing for classic paraneoplastic antibodies using a neuronal antigens profile for CV2/CRMP5, Ma2, Ri, Yo, Hu, and amphiphysin (Neuronal Antigens Profile PLUS; Euroimmun AG) were performed in serum.

Statistical Analysis

The Fisher exact test was performed for comparison of categorical variables, and the Mann-Whitney test was used for continuous variables. Statistical significance was considered at $P < .05$. JMP, version 11.2.0 (SAS Institute Inc), was used. Data analysis was conducted between July 15, 2015, and January 18, 2016.

Results

Clinical Features, Treatment, and Complications

Ten of 15 patients (67%) were female; the median age at disease onset was 21 years (range, 14–46 years). Twelve patients (80%) presented with typical anti-NMDAR encephalitis,[1–3] beginning with acute onset of psychiatric symptoms and followed by decreased level of consciousness with seizures, hypoventilation, bizarre orofacial-limb dyskinesias, and autonomic features. Two patients (13%) developed isolated convulsive seizures, and 1 patient (7%) presented with progressive hemiparesis. Nine patients (60%) required mechanical ventilatory support (median, 10 weeks; range, 2–40 weeks); 4 of these 9 patients developed serious complications. The median hospitalization was 4.1 months (range, 1.1–18.2 months); 5 patients (33%) required long-term hospitalization (range, 9.3–18.2 months).

Symptomatic treatment, including intravenous sedation (propofol, midazolam hydrochloride, or thiamylal sodium) was used in 14 patients. First-line immunotherapies were administered in 13 patients (87%) (intravenous high-dose methylprednisolone, 13; intravenous immunoglobulin, 11; and plasma exchange, 4), intravenous cyclophosphamide in 4 patients (27%) (started 1 year after disease onset in patient 9), and long-term oral immunotherapy (>3 months) in 6 individuals (40%). Two patients (13%) did not receive immunotherapy. In 5 patients (33%) an ovarian teratoma was found and removed at disease nadir (n = 1), 9 months after symptom onset (n = 1), or after recovery (n = 3).

Antibody Findings—Cerebrospinal fluid was available from 13 patients, and all samples were positive for NMDAR antibodies (eTable in the Supplement). Serum was available from all 15 patients; 13 samples were positive for NMDAR antibodies. In 2 patients (7 and 11), the antibodies were present only in CSF. Myelin oligodendrocyte glycoprotein antibodies were detected in 2 of 2 patients examined because one had a history of acute disseminated encephalomyelitis (patient 8) and the other had demyelinating lesions (patient 12). Glycine receptor antibodies were also examined in 2 patients (9 and 14) who developed cerebellar atrophy; however, the antibodies were not found. No other antibodies to cell surface or synaptic proteins or to classic paraneoplastic antibodies were detected.

MRI Findings—Multiple brain MRI studies were obtained and chronological changes were assessed after a median follow-up of 20 months (range, 2–90 months). During the acute stage (within 3 months of symptom presentation), MRIs indicated several different abnormalities in 8 patients (53%), including symmetric medial temporal or thalamic lesions, transient splenial lesions, multifocal demyelinating lesions, and gadolinium enhancement (eFigure 1 in the Supplement).

In 5 patients (33%) (patients 4, 5, 7, 9, and 14), DCA developed 1 to 2 months after symptom onset and reached a plateau at 6 to 16 months (Figures 1, 2, 3, and 4 and eFigure 2 in the Supplement). In 2 of the 5 patients (9 and 14), cerebellar atrophy insidiously developed with DCA; it started 1 to 2 months after symptom onset and progressed for more than 12 months (Figure 4 and eFigure 2 in the Supplement). Follow-up MRIs demonstrated reversal changes in the DCA of 3 patients (4, 5, and 7) who had a good long-term outcome; these changes began approximately 1 year after symptom onset, and the brain volume eventually returned to almost baseline level at the last follow-up MRI (90, 70, and 24 months, respectively). In patient 7, who did not receive immunotherapy and remained unresponsive for 8 months, a reversal process was apparently accelerated by the initiation of combined immunotherapies (Figure 3). In patients 9 and 14, who remained highly disabled, DCA also partially reversed as indicated at the last follow-up MRIs compared with those obtained at the disease nadir; however, cerebellar atrophy remained unchanged or slightly progressed at the last follow-up (Figure 4 and eFigures 2 and 3 in the Supplement).

Factors Associated With Poor Long-term Outcome—Long-term outcome, assessed after a median follow-up of 68 months (range, 10–179 months), was good in 13 patients (including patients 4, 5, and 7, who had serious complications and DCA) and poor in the other 2 patients (9 and 14, who developed marked cerebellar ataxia) (eTable in the Supplement). Patient 4 had bilateral above-the-knee amputation for arterial thrombosis associated with disseminated intravascular coagulation, and she was in an apallic state for the first 18 months. This patient is remarkable because she progressively improved; 12 years after symptom onset, she became independent in activities of daily living and continues her employment 15 years after onset, with mild dyscalculia being the only neurologic deficit (29 of 30 on the Mini-Mental State Examination,[17] with higher scores indicating better cognitive function; thus, her outcome is considered good). Her mRS score of 4 was caused by the bilateral leg amputation due to arterial thrombosis; otherwise, she had a dramatic neurologic recovery. Patient 5 returned to her job 3 years after disease onset and continues actively working without any neurologic problems 13 years after presentation (mRS score, 0). Patient 7 also returned to work 5 years after disease onset and continues employment, but she has short-term memory loss at 7 years (29 of 30 on the Mini-Mental State Examination; mRS score, 2). In contrast, patients 9 and 14 (last follow-up at 4.6 and 5.7 years after disease onset, respectively) continue to have limb and truncal ataxia along with residual cognitive deficits; patient 9 is able to ambulate with a walker (mRS score, 4), but patient 14 is wheelchair bound and has severe dysphonia, dysphagia, limb dystonia, and slow saccade without nystagmus (mRS score, 5).

Poor long-term outcome was associated with cerebellar atrophy (2 of 2 vs 0 of 13 patients; $P = .01$) but not with DCA, serious complications, ventilatory support, or prolonged

hospitalization. The 5 patients who developed DCA had longer hospitalizations (median, 11.1 vs 2.4 months; $P = .002$), required more frequent ventilatory support (5 of 5 vs 4 of 10 patients; $P = .04$), and developed more serious complications (4 of 5 vs 0 of 10 patients; $P = .004$) than did those who did not develop DCA, but there was no significant difference in the duration of ventilatory support (median, 24 vs 8 weeks) or other factors.

Correlation between brain atrophy and antibody titers was not assessed in this study. However, in the 2 patients with cerebellar atrophy, the CSF antibody titers were low (1:80 at presentation and 1:160 at 1-year follow-up) in patient 9 and no longer detectable at 2 years and 3 years in patient 14. In contrast, despite high CSF antibody titers (1:1280 at presentation), no brain atrophy occurred in patient 15 who received intravenous cyclophosphamide at the early stage of the disease.

Discussion

This study shows that the development of progressive cerebellar atrophy in patients with anti-NMDAR encephalitis is associated with limited clinical recovery. This finding is in contrast to the development of DCA, which occurred in 33% of the patients but was usually reversible and did not affect the clinical outcome.

A variety of MRI findings have been reported[1–4,9] in patients with anti-NMDAR encephalitis, including white matter changes[18]; however, most studies are focused on changes in the acute stage of the disease. Few studies have addressed the long-term MRI changes.[6,7] Reversible brain atrophy was previously reported[7] in 2 of our patients (patients 4 and 5) who developed severe dyskinesias, for which they were treated with anesthetics for 6 to 7 months as well as first-line immunotherapy. Despite marked DCA, both patients slowly recovered 3 to 4 years after symptom onset, and MRIs obtained 6 to 7 years after symptom onset showed that the brain atrophy had reversed. Since then, an additional case has been reported,[19] but the frequency of brain atrophy is unknown.

One-third of the patients in the present study developed DCA, and we were able to follow their long-term outcome. A significant finding is the reversibility of DCA in 3 patients and their gradual recovery of cognitive function at the last follow-up. This recovery resulted in no neurologic deficits in one patient, mild dyscalculia in another, and short-term memory loss in the third individual (patient 7). This short-term memory loss is likely related to bilateral medial temporal T2/FLAIR high signals at presentation (Figure 3) but not to DCA itself. Thus, DCA may not imply a poor long-term outcome.

The mechanisms of DCA remain largely unknown. Potential risk factors include systemic complications (heart failure[20] and septic shock[21]), malnutrition,[22,23] status epilepticus,[24,25] prolonged use of corticosteroids,[26] long-term exposure to various antiepileptic agents,[27,28] and propofol infusion syndrome.[29] Our patients with DCA developed more serious complications and required ventilatory support more frequently than did those without DCA. Indeed, all 5 patients required mechanical ventilatory support, but the development of DCA was not significantly associated with the duration of ventilatory support. Diffuse cerebral atrophy subsequently reversed, with gradual recovery of symptoms in 3 patients and partial

recovery in 2 patients with cerebellar atrophy. None of the 5 patients received second-line immunotherapy, which is currently used for patients who are refractory to first-line immunotherapies.[3] This finding is in contrast to the other 10 patients of the present study who received aggressive treatment when needed. In patient 7, a reversal process of DCA was accelerated by immunotherapy.

NMDAR antagonists (eg, phencyclidine[30] and ketamine[31]) have been implicated in the development of brain atrophy. The antibodies of patients with anti-NMDAR encephalitis bind to the aminoterminal domain[32] rather than to the ligand-binding domain, causing receptor internalization.[33] At this time, it is unclear whether internalization of the receptors is a cause of atrophy.

Although MRI cerebellar abnormalities (eg, increased FLAIR signal or transient enhancement) have been reported[2] in 6% of patients with anti-NMDAR encephalitis and a case of severe cerebellar ataxia has been presented,[34] progressive cerebellar atrophy has not been described in this disease. In our 2 patients, MRI showed progressive dilatation of the sulci of the cerebellar cortex, with relative sparing of subcortical tissue (eFigure 3 in the Supplement), and was associated with a poor clinical outcome. The cerebellar atrophy was not associated with prolonged ventilatory support, serious complications, delays in initiation of immunotherapy, or type of treatment. In contrast to DCA that was reversible, the cerebellar atrophy was irreversible. Therefore, the underlying mechanisms of cerebral and cerebellar atrophy may be different.

In the cerebellum, the IgG NMDAR antibodies predominantly bind to granular cells, but not to Purkinje cells, because of the lack of expression of NMDAR on Purkinje cells. Moreover, cerebellar ataxia is not a predominant symptom in most patients with anti-NMDAR encephalitis. Postmortem studies[1] have not shown significant loss of Purkinje cells, but one patient with fulminant progressive encephalomyelitis who had overlapping glycine and NMDAR antibodies showed involvement of the cerebellar Purkinje cells.[35] Our patients did not have additional antibodies reacting with the cerebellum, including glycine receptor antibodies; in fact, the pattern of serum and CSF reactivity was similar to that of patients with typical anti-NMDAR encephalitis who do not develop cerebellar atrophy.

Our study has the limitation of being retrospective and based on only 15 patients. One might argue that cerebellar atrophy occurred in 2 of the 4 patients with severe systemic complications and, therefore, these complications were the cause of the atrophy. We cannot rule out this possibility or that metabolic factors may have contributed to the cerebellar atrophy.

Conclusions

In anti-NMDAR encephalitis, DCA can be reversible and does not imply a poor clinical outcome; however, cerebellar atrophy was irreversible and associated with poor outcome. Studies are needed to confirm whether the progressive development of cerebellar atrophy is associated with poor outcome and could potentially be used as a prognostic biomarker in anti-NMDAR encephalitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Does the development of brain atrophy predict poor outcome in anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis?

Findings

In this retrospective series of 15 patients with NMDAR encephalitis, diffuse cerebral atrophy occurred in 5 individuals, 2 of whom had associated cerebellar atrophy. The brain atrophy was reversible in 3 patients (accompanied by clinical improvement) and partially reversible in the 2 individuals with cerebellar atrophy; however, the occurrence of progressive cerebellar atrophy was associated with poor long-term clinical outcome.

Meaning

In anti-NMDAR encephalitis, diffuse cerebral atrophy does not imply irreversible brain damage or poor clinical outcome; in contrast, cerebellar atrophy appears to be associated with poor long-term outcome.

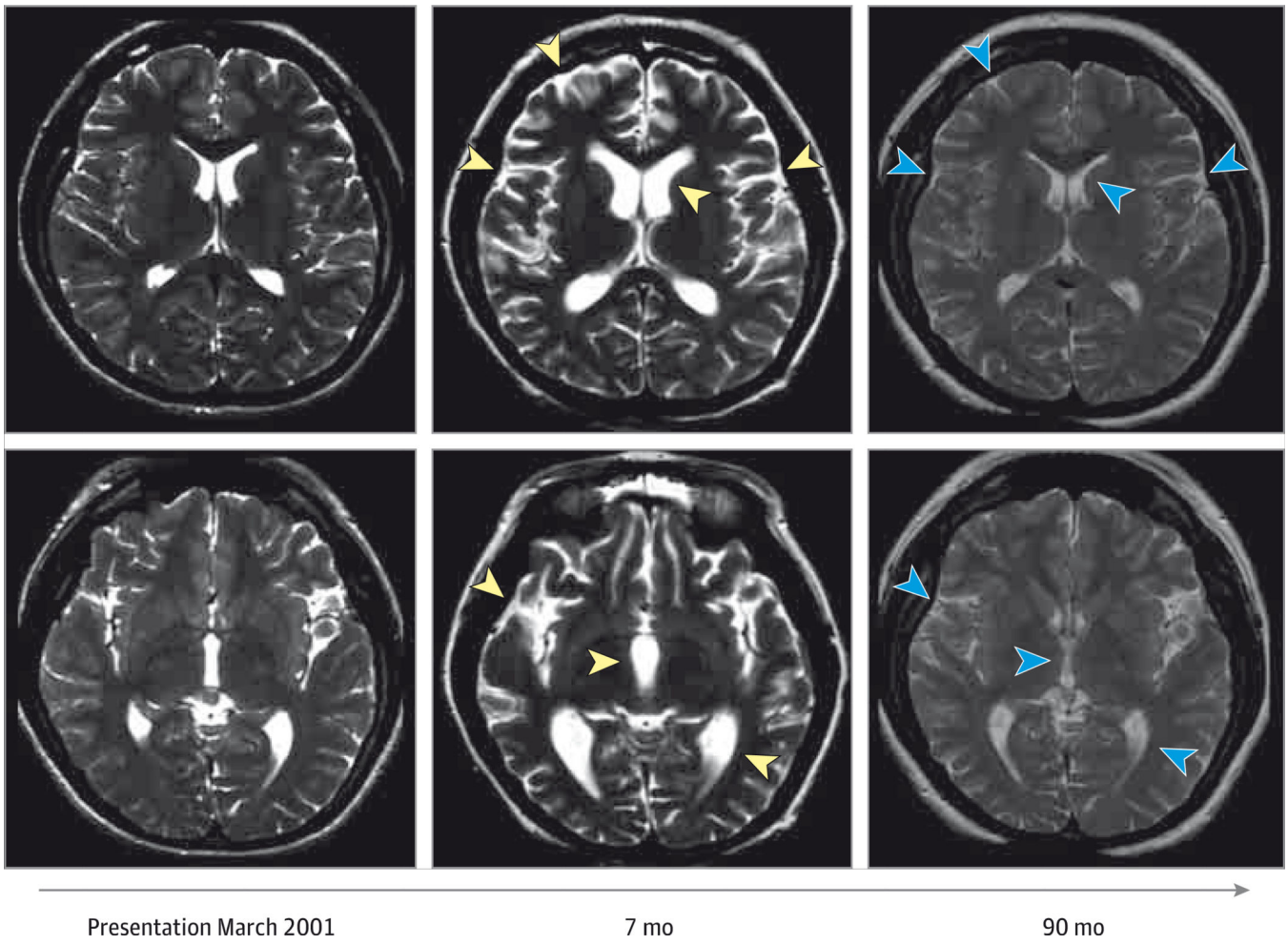

Figure 1. Reversal of Diffuse Cerebral Atrophy in Patient 4

Follow-up T2-weighted magnetic resonance imaging (MRI) shows progressive brain atrophy, which was first noted at 1.5 months and became prominent at 7 to 11 months. The last follow-up MRIs obtained at 90 months show reversal of the diffuse atrophy. Note marked dilatation of the third ventricle, the anterior horn, and the cerebral sulci (yellow arrowheads), and a reversal of dilated ventricles and cerebral sulci (blue arrowheads).

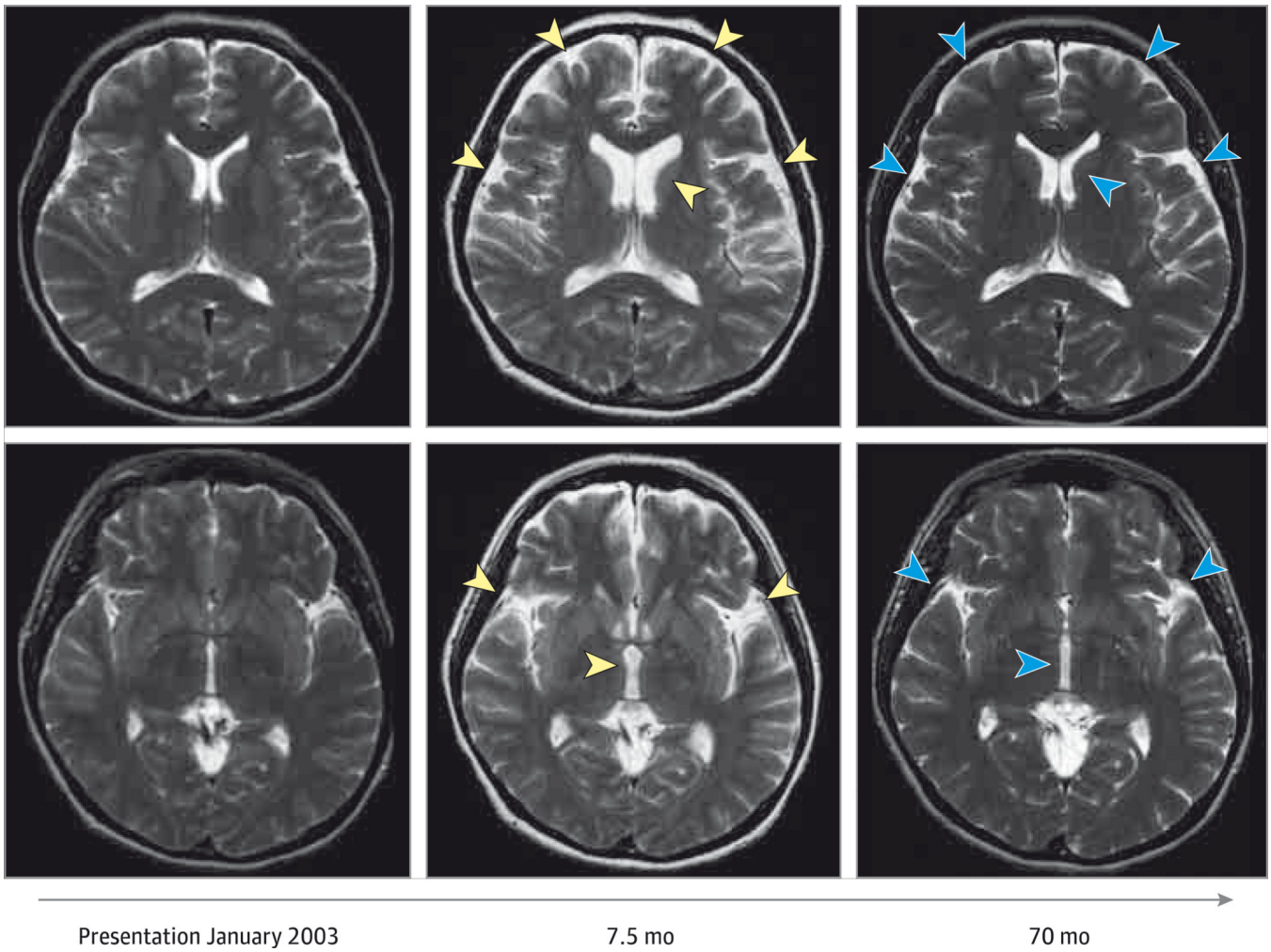

Figure 2. Reversal of Diffuse Cerebral Atrophy in Patient 5

Follow-up T2-weighted magnetic resonance imaging (MRI) shows mild diffuse cerebral atrophy, which was first noted at 4 months and became prominent at 6 to 7.5 months. However, follow-up MRIs at 70 months show reversal of the brain atrophy. Note mild dilatation of the third ventricle, the anterior horn, and the cerebral sulci, including the Sylvian fissure (yellow arrowheads), and a reversal of dilated ventricles and cerebral sulci (blue arrowheads).

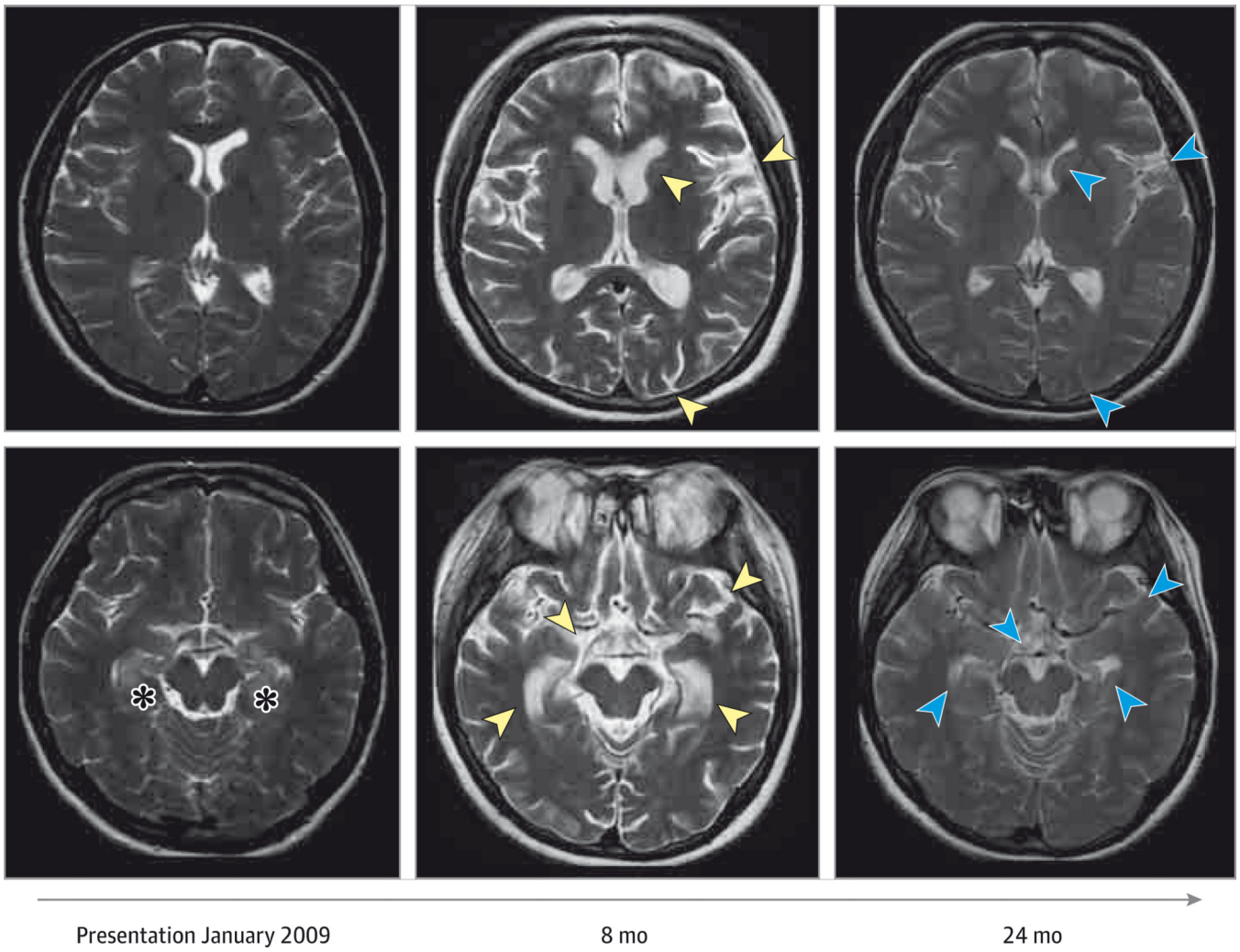

Figure 3. Relatively Quick Recovery of Diffuse Cerebral Atrophy in Patient 7

Initial magnetic resonance imaging (MRI) shows symmetric T2 hyperintense signals in the medial temporal lobes (asterisks). Follow-up T2-weighted MRIs show diffuse cerebral atrophy with dilatation of the cerebral sulci and the ventricle, which was seen at 1 month and became prominent at 5.5 to 8 months (yellow arrowheads). However, subsequent MRIs show reversal of the brain atrophy, which ultimately returned to baseline brain level at the 24-month follow-up examination. Note recovery of dilated cerebral sulci as well as dilated ventricles (blue arrowheads).

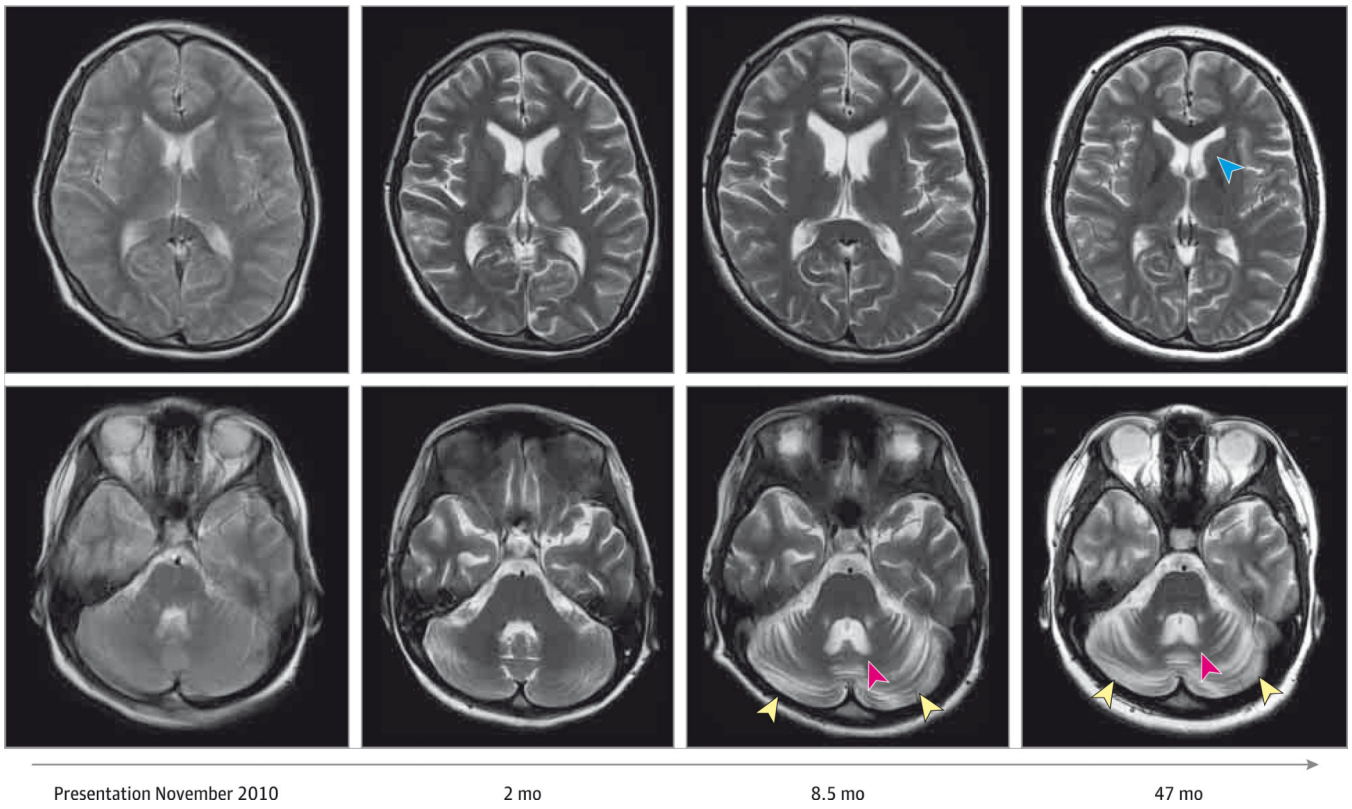

Figure 4. Progressive Cerebellar Atrophy and Partial Recovery of Cerebral Atrophy In Patient 9

Follow-up T2-weighted magnetic resonance imaging (MRI) shows development of diffuse cerebral atrophy and progressive cerebellar atrophy. Cerebral and cerebellar atrophy are seen at 2 months and became prominent at 8.5 months. Since then, diffuse cerebral atrophy partially reversed with recovery of anterior horn dilatation (light blue arrowhead), but cerebellar atrophy remained unchanged at 47 months. Note progressive dilatation of the fourth ventricle (red arrowheads) and dilated cerebellar sulci (yellow arrowheads).